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Arkivoc **2021**, part v, 0-0
to be inserted by editorial office

An enantiopure building block for naturally occurring hydroporphyrins and vitamin B_{12} from Hagemann´s ester

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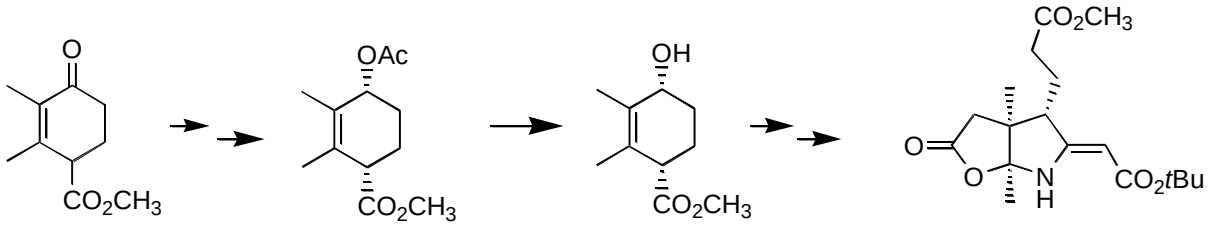
Dedicated to Peter A. Jacobi

Received 11-19-2020 **Accepted** 12-13-2020 **Published on line** 12-20-2020

Abstract

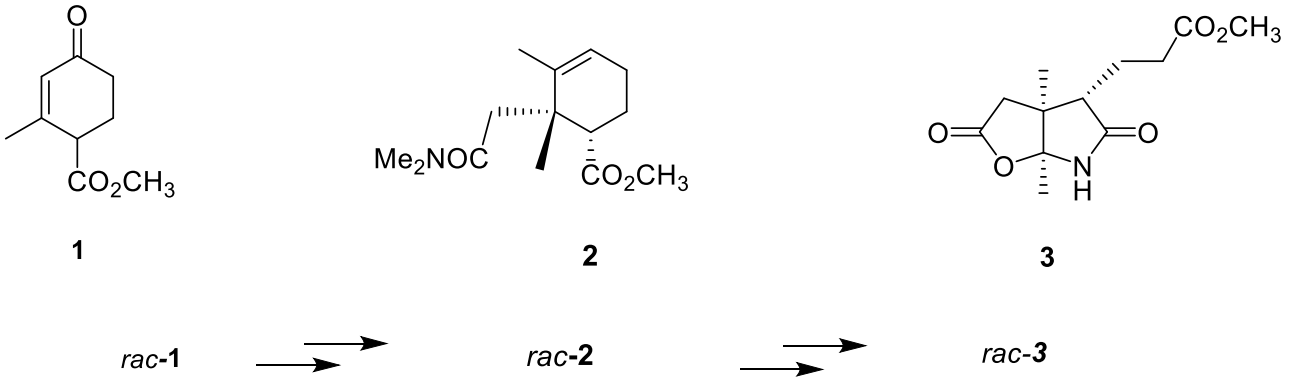
Enantiomerically pure ring building block for naturally occurring hydroporphyrins and possibly vitamin B_{12} was synthesized starting from methylated Hagemann´s ester. Originally, this ester was utilized to investigate preparation of ring building blocks for vitamin B_{12} in Eschenmoser´s and Woodward´s syntheses. Hagemann´s ester furnished methyl 4-acetoxy-2,3-dimethylcyclohex-2-en-1-carboxylate in racemic form. Kinetic enzymatic resolution of the cyclohexene acetate led to the enantiopure hydroporphyrin building block methyl {(1*S*,2*S*,5*S*,3*Z*)-3-(2-*t*-butoxy-2-oxoethylidene)-1.5-dimethyl-7-oxo-4-aza-6-oxabicyclo[3.3.0]oct-2-yl}-2-propionate.



Keywords: Hagemann´s ester, enzymatic chiral resolution, Meerwein-Eschenmoser-Claisen rearrangement

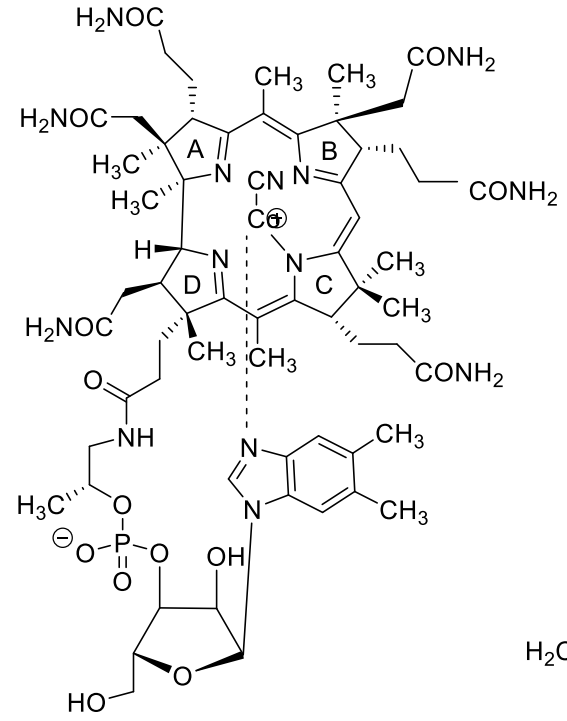
Introduction

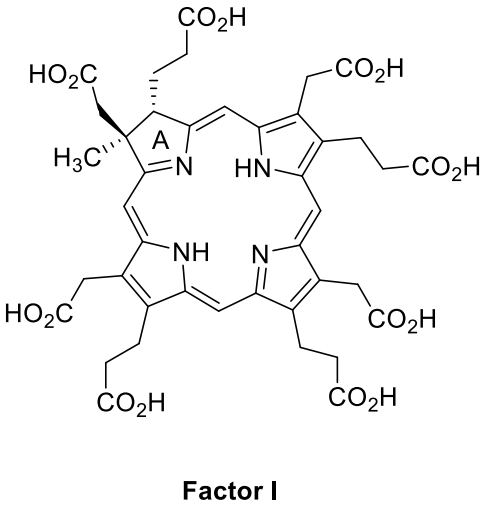
Since its discovery in 1893 Hagemann´s ester *rac*-**1** has become an important building block in organic synthesis.[1,2] Based on its unique multifunctional reactivity Hagemann´s ester *rac*-**1** was in particular utilized as starting material for numerous syntheses of natural products.[2] Also in the course of vitamin B_{12} syntheses[3-7] Hagemann´s ester was successfully applied by Eschenmoser for synthesis of a building block in racemic form (*rac*-**3**) for rings A and B of the macrotetracycle.[3,8,9] Though this approach (Scheme 1) was finally not used in favour of an alternative ring A,B synthesis for vitamin B_{12}, its key step established a novel method for Claisen rearrangements.[3,8-10] Today this rearrangement is known as the Meerwein-Eschenmoser rearrangement[8-10] which represents a gentle synthetic tool together with Johnson´s *ortho*-ester Claisen rearrangement[11] and Ireland´s ester enolate rearrangement.[12]

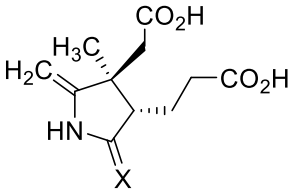


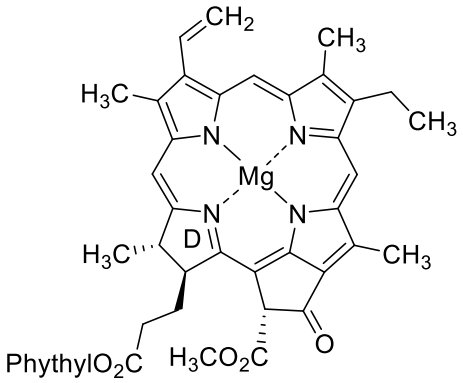
Scheme 1. Eschenmoser´s amide acetal approach leading to a lactone lactam intermediate *rac*-**3** for Vitamin B_{12} synthesis.[3,8,9]

Several hydroporphyrins, among them factor I and sirohydrochlorin (Figure 1), were discovered in the post-vitamin B_{12} era.[13-19] These hydroporphyrins and also chlorophyll *a* exhibit partial structures identical or closely related to structure patterns present in vitamin B_{12}. Therefore, building blocks applied in vitamin B_{12} synthesis could play a role as suitable common educts for the preparation of hydroporphyrins. To achieve a common building block with the desired *absolute configuration* we considered transformation of the original Hagemann´s ester approach from vitamin B_{12} synthesis into a *chirogenic enantioselective* route.









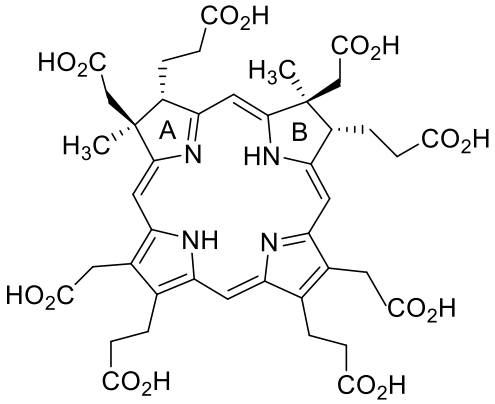
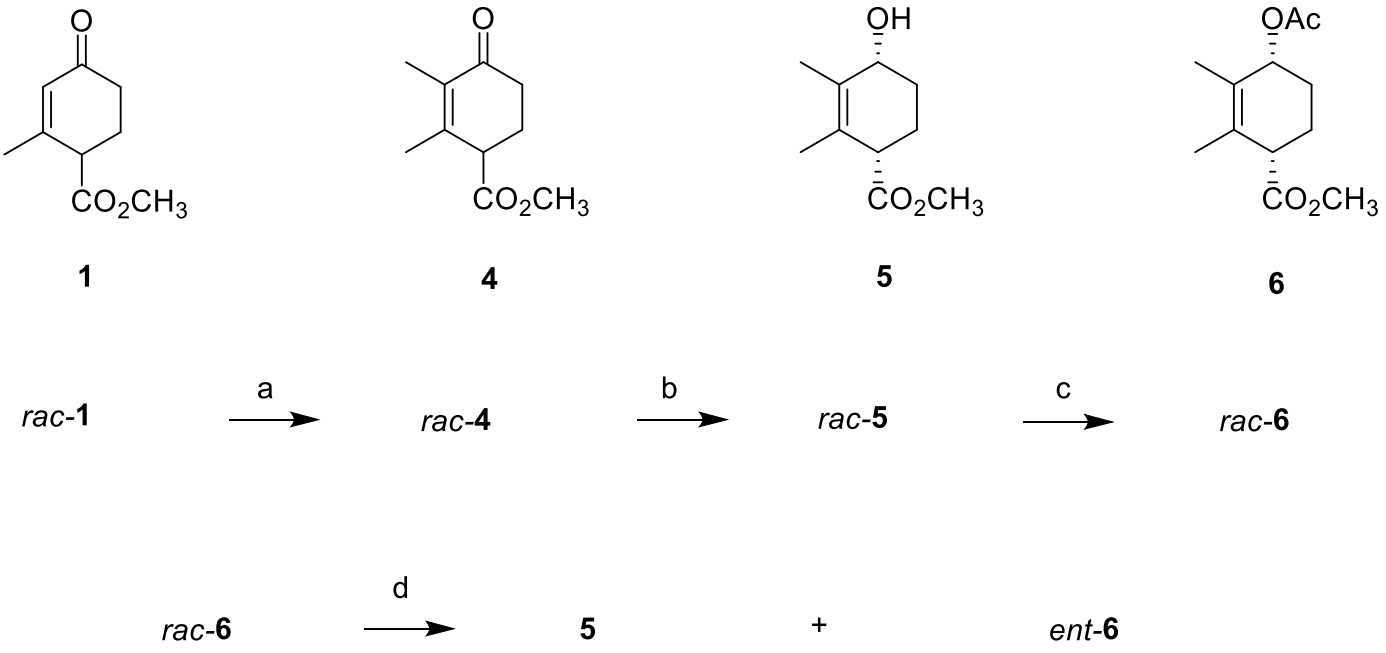


Figure 1. A common building block for naturally occurring tetrapyrrolic pigments.

Results and Discussion

Hagemann´s ester can be considered as a vinylogous β-ketoester which gives rise to an equilibrium between both of its enantiomers **1** and *ent*-**1** interchanged *via* keto-enol tautomerization, thus consisting of a racemic mixture *rac*-**1**.[20] Facile enolate formation of *rac*-**1** enables methylation in position 3 to give methyl derivative *rac*-**4** (Scheme 2). Reduction of methylated Hagemann´s ester *rac*-**4** with lithium tri-*tert*-butoxyaluminium hydride led with high diastereoselectivity to a racemic mixture of *cis*-alcohol *rac*-**5**. In the former vitamin B_{12} work *cis*-configuration of *rac*-**5** was established by its lactone formation which is only possible with the *cis*-

isomer.[9] We were able to obtain crystals of *rac*-**5** suitable for X-ray analysis which also confirmed *cis*-configuration of *rac*-**5** (see Supplementary Material). To achieve enantiomerically pure alcohol **5** an enzymatic kinetic resolution of *rac*-**5** was performed. The acetoxy derivative *rac*-**6** was obtained with high yield which then underwent enzymatic hydrolysis to give desired enantiomerically pure (ee > 98%) alcohol **5** and unchanged acetoxy derivative *ent*-**6**.



Scheme 2. Synthesis of enantiomerically pure Hagemann´s alcohol **5**. Reaction conditions.
(a) NaH, THF, -78 °C, then CH_3I, 2h (94%).[3,9] (b) Li[Al(*t*-$BuO)_3H$], ether, rt, 24 h (66%).[3,9] (c) Ac_2O, NEt_3, DMAP, THF, 0 °C, 3 h (95%). (d) Pig liver esterase (PLE: E.C.3.1.1.1), MeOH, pH 7 phosphate buffer, 1N KOH, 25 °C, 48 h (**5**: 33%, ee 98%; *ent*-**6**: 41%, ee not determined).

Alcohol **5** was transformed into its *N*-tosylproline derivatives **15** for determination of its enantiopurity (Figure 2). ^{1}H NMR spectrum of a diastereomeric mixture of *N*-tosylproline derivatives **14**/**15** derived from *rac*-**5** shows two methyl ester signals, one for each diastereomer. In contrast, for *N*-tosyl derivative **15** formed from **5** only one signal was observed thus confirming its enantiopurity. Absolute configuration of alcohol **5** follows from its further transformation into compounds of known absolute configuration in the course of subsequent synthesis. Conservation of enantiopurity of intermediates in the course of synthesis was proven by NMR experiments with chiral shift reagents (Figure 2).

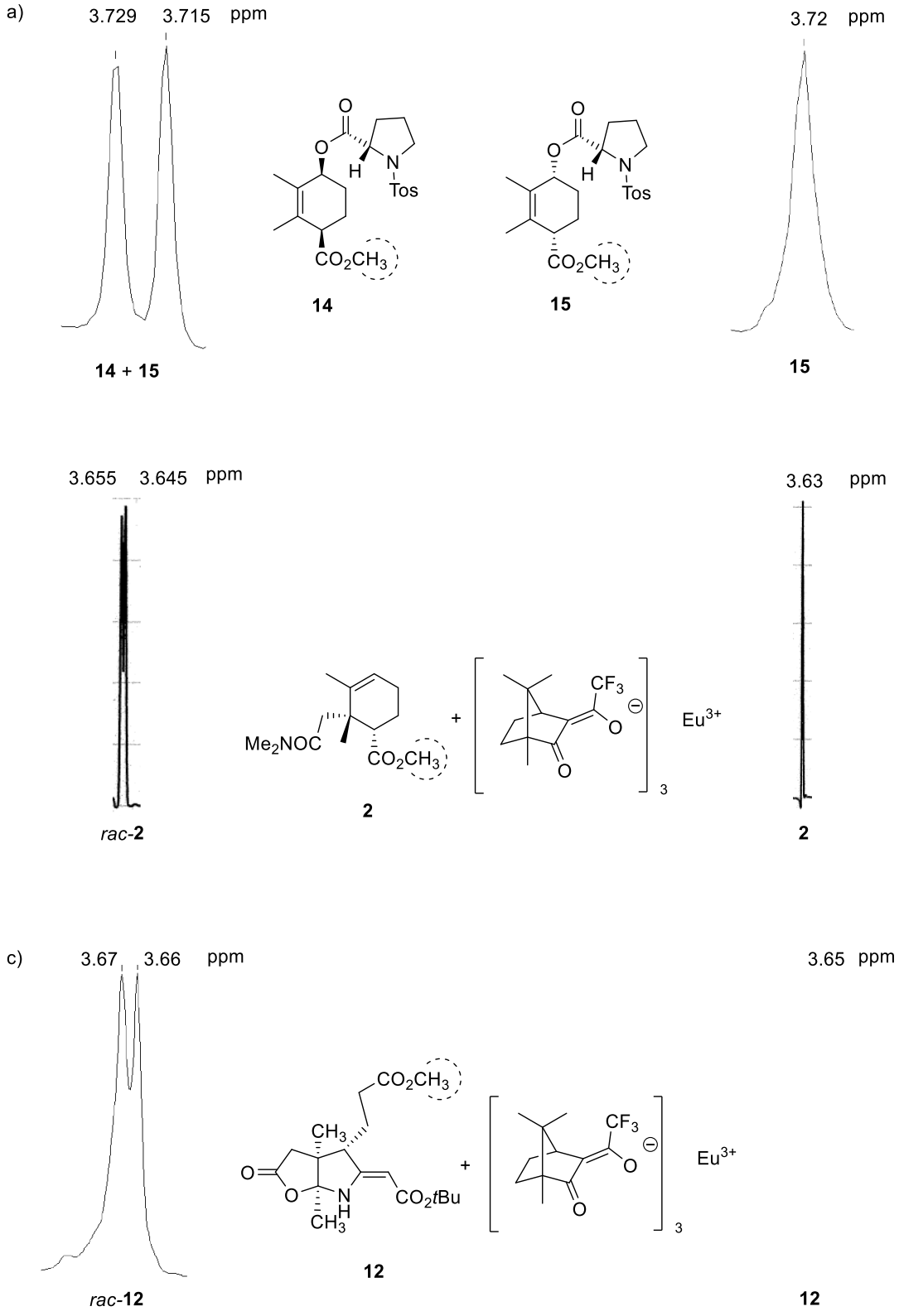
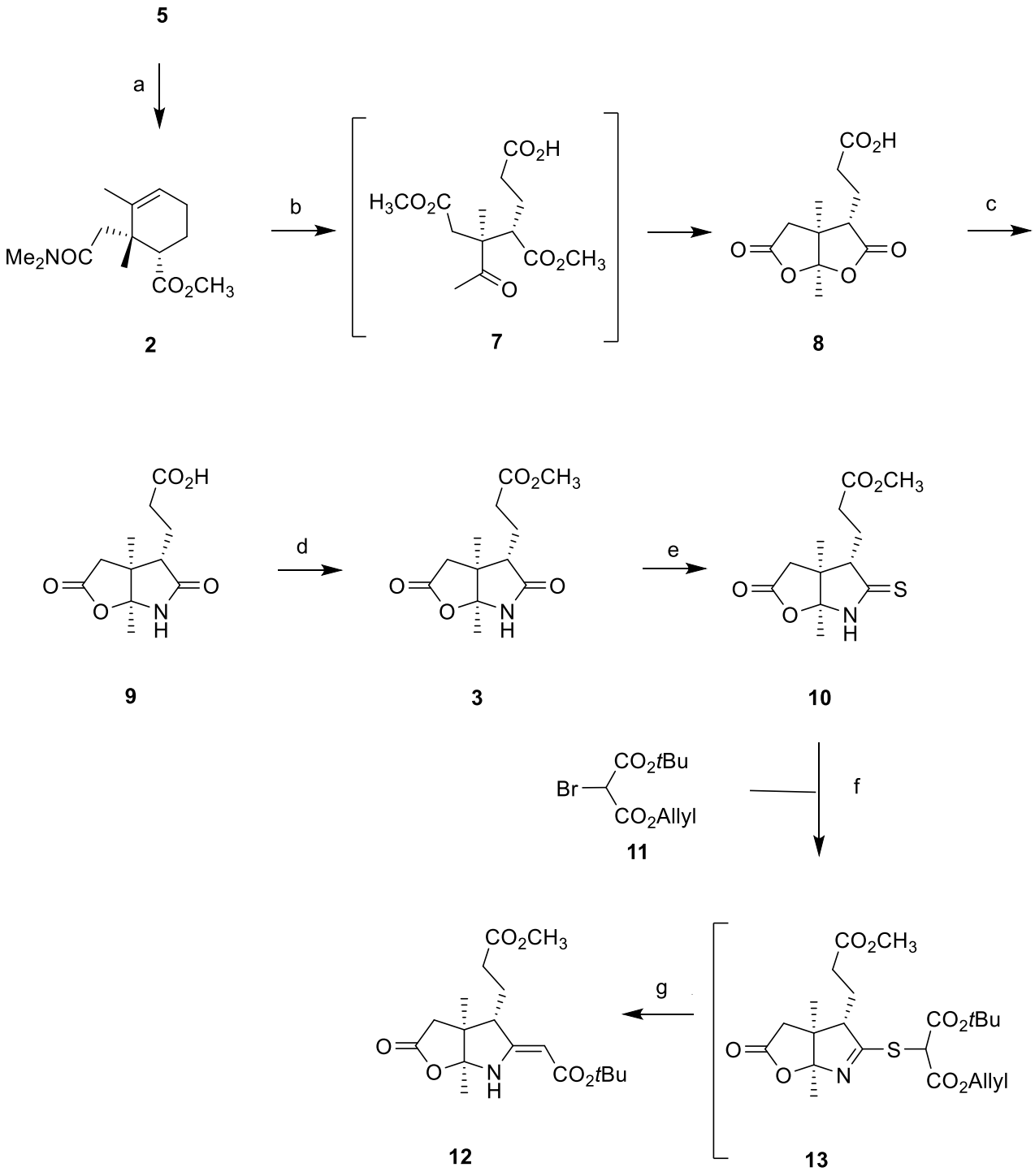


Figure 2. (a) Determination of enantiomeric excess of *cis*-alcohol **5** by ^{1}H NMR of its diastereomeric tosyl proline derivatives **14** and **15** (methyl ester signals). (b) Determination of enantiomeric purity of rearrangement product **2** by ^{1}H NMR shift experiment with chiral Eu(TFC)$_3$ (methyl ester signals). (c) Determination of enantiomeric purity of building block **12** by ^{1}H NMR shift experiment with chiral Eu(TFC)$_3$ (methyl ester signals).

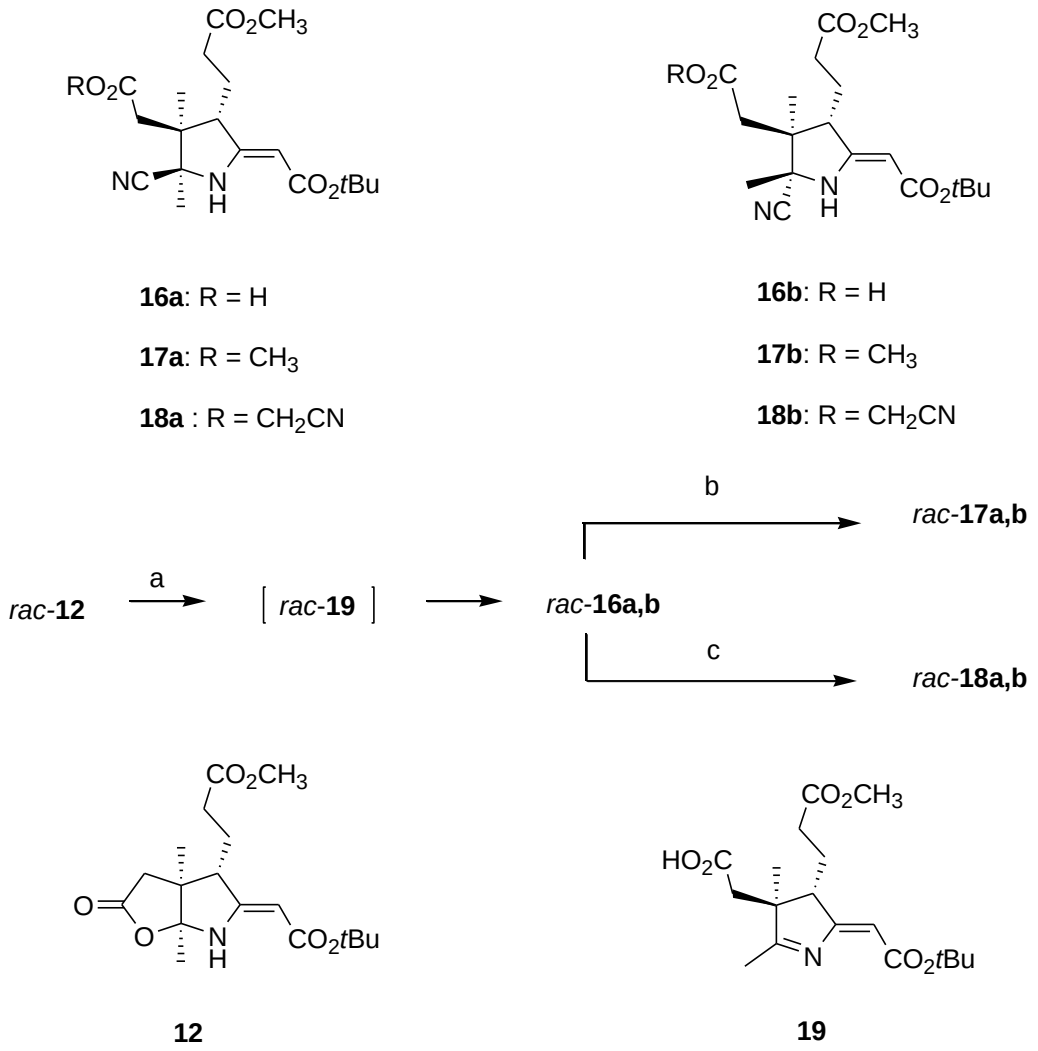


Scheme 3. Synthesis of building block **12**. (a)-(d) Slightly modified reaction conditions adopted from vitamin B_{12} synthesis.[3,9] (a) $MeC(OMe)_2NMe_2$, *p*-xylene, Ar, reflux, 3 h (6%, ee > 99%). (b)(i) O_3/O_2, MeOH, -80 °C; (ii) 35 percent H_2O_2, HCO_2H, reflux, 3 h (51%). (c) NH_3 MeOH, 0 °C, 70 h. (d) HCl gas, rt, (58 % rel. **8**) or BOP, NEt_3, MeOH, THF, rt, 24 h (64% rel. **8**, ee 98%). (e) Lawesson reagent [2,4-bis(*p*-methoxyphenyl)-1,3-dithiaphosphetane-2,4-disulfide], THF, Ar, reflux, 45 min (**10**: 84%, ee > 99%; 2-*epi*-**10**: 8.4%). (f) **10** + **11**, DBU, MeCN, Ar, 0 °C, 25 min. (g)(i)$P(OEt)_3$, Ar, 80 °C, 18 h; (ii) Pd $(PPh_3)_4$, piperidine, THF, Ar, rt, 4 h (60% rel. **10**, ee > 99%).

Enantiomerically pure alcohol **5** underwent Meerwein-Eschenmoser-Claisen rearrangement with *N,N*-dimethylacetamide dimethyl acetal to give cyclohexene carboxylate **2** (Scheme 3). Rearrangement product **2** is completely (> 99%) enantiopure as confirmed by NMR experiments with chiral europium shift reagent [Eu(TFC)$_3$] (Figure 2). Formation of a trace amount of diastereomeric *trans*-**2** can be attributed to equilibration of the carbomethoxy group induced by the slightly basic rearrangement reaction conditions or by a minimally decreased streoselectivity of the rearrangement process itself. Since *trans*-diastereomer of **2** is formed in that case enantiopurity of **2** is not affected.

Ozonolysis of *N,N*-dimethylamide ester **2** followed by oxidative workup in the presence of acid cleaved the cyclohexene double bond giving keto and a carboxylic acid functions. Proposed intermediate **7** afforded dilactone acid **8** which was further transformed *via* lactone lactam **9** into lactone lactam ester **3**. The whole reaction sequence was elaborated during work on vitamin B$_{12}$ [3,8-9] to give racemic lactone lactam ester *rac*-**3** (*rac*-**2** – *rac*-**7** – *rac*-**8** – *rac*-**9** – *rac*-**3**). Therefore a detailed characterization of intermediates was not performed. However, for dilactone carboxylic acid *rac*-**8** and its epimer *epi*-*rac*-**8** crystals suitable for X-ray analysis were obtained (see Supplementary Material). As mentioned before, for syntheses of vitamin B$_{12}$[3-5] an alternative approach was applied to achieve enantiopure lactone lactam ester **3**. Comparison of lactone lactam **3** derived from allylalcohol **5** with **3** from vitamin B$_{12}$ synthesis revealed its absolute configuration and therefore those of intermediates of the synthesis route. Conversion of lactam **3** into its thiolactam **10** was originally achieved by treatment with P$_4$S$_{10}$.[3,21,22] Actually, sulfuration was performed with Lawesson´s reagent to give a separable 10 : 1 mixture of **10** and its epimer 2-*epi*-**10**. Thiolactam **10** was transformed by the sulfide contraction method[3,22,23] into the target compound **12**. Thiolactam **10** reacted with bromo malonic diester **11**[24-26] in the presence of DBU to yield coupling product **13**. Crude **13** was heated in triethyl phosphite for sulfur extrusion and contracted diester intermediate was allowed to react further without purification to give **12** with allyl ester cleavage and decarboxylation. Allylic ester function is selectively cleaved with piperidine catalyzed by tetrakis(triphenylphosphane)palladium(0) and the carboxylic acid decarboxylates spontaneously *via* an intermediate imine tautomer.[25,27] As observed in previous investigations[24-26,28] **12** is formed exclusively with *Z*-configuration at the double bond, due to a stabilizing intramolecular hydrogen bond between ring NH and ester carbonyl group. X-ray structure confirmed relative configurations of all the stereogenic centers of **12**. Enantiopurity was checked by NMR shift experiments with [Eu(TFC)$_3$](Figure 2) which demonstrated that methyl ester signals of *rac*-**12** were split off whereas **12** shows only one methyl ester signal as expected.

Cleavage of the γ-lactone ring of **12** with potassium cyanide in methanol should give more stable lactam derivatives compared to lactone lactam (Scheme 4). Whereas imine derivative **19** is formed by lactone ring cleavage of **12** under gentle basic reaction conditions, cyanide elimination from **16**-**18** requires drastic reaction conditions. Therefore cyano adducts could be beneficial for further reaction steps in the course of syntheses. Cyanide addition was performed with *rac*-**12** to furnish a diastereomeric mixture of cyano adducts *rac*-**16a** and *rac*-**16b** in an 8 : 2 ratio. Prior to cyanide addition the γ-lactone ring is cleaved to form an imine intermediate *rac*-**19**. As demonstrated for a similar case cyanide attack to imine intermediate *rac*-**19** is directed by the carboxylic acid function preferring *cis*-isomer *rac*-**16**.[26] The formed acetic acid side chain was esterified with diazomethane (*rac*-**17a,b**) resp. with chloroacetonitrile (*rac*-**18a,b**). In the latter case the differentiation of the acid side chain is preserved for possible subsequent regioselective transformations.



Scheme 4. (a) KCN, MeOH, Ar, 20 h (*rac*-**16 a,b**: 55.6% mixture of epimers; *rac*-**12** (reisolated educt): 40%). (b) CH_2N_2, ether, MeOH, rt, 10 min (68% mixture of epimers). (c) NEt_3, CH_2Cl_2, then add. of $ClCH_2CN$, Ar, rt, 18 h (60% mixture of epimers).

Conclusions

An enantioselective synthetic route forms lactam lactone diester **12** in seven synthesis steps starting from methylated Hagemann´s ester *rac*-**4** in overall yield of 9.4%. Key step for preparation of enantiomerically pure Hagemann´s alcohol **5** is a kinetic enzymatic resolution of acetoxy derivative *rac*-**6**. Enantiopurity of alcohol **5** (> 98%) is completely preserved along the synthetic route.

Experimental Section

General. Starting materials were prepared either according to literature procedures or were purchased from Fluka, Merck, Acros Organics or Sigma Aldrich and used without further purification. All solvents were purified and dried by standard methods. All reactions were carried out under argon. Melting points are not corrected.

TLC: Silica gel plates (Riedel de Haen, silica gel 60 F 254; Macherey-Nagel, Polygram SIL G/UV 254). Column chromatographic separations were performed on silica gel (ICN Biomedicals, 32-63 μm, 60 Å) and aluminium oxide (ICN Biomedicals Alox N activity II). UV/Vis: Specord 210 Plus spectrometer, Analytic Jena). Optical Rotation: Perkin-Elmer 243 polarimeter. CD: JASCO J-600 spectropolarimeter. IR: Perkin-Elmer Paragon 500 FT-IR spectrometer. NMR: Bruker DPX-200 AVANCE, Bruker AM 360 spectrometer, Bruker AMX spectrometer and Bruker 600 AVANCE neo. All chemical shifts were referenced to TMS lock signal. Exact assignment of proton signals in ^{1}H NMR spectra was achieved by two dimensional H,H-COSY and NOESY experiments. MS: Finnigan MAT 8200, MAT 95, MAT 95 XL spectrometer [E (70 eV) and DCI (NH_3, 8 mA/s)] and Esquire LC, Bruker Daltonic. HRMS: Finnigan MAT 8200 spectrometer according peak matching method. X-ray crystal structure analysis: The crystallographic data were collected with Siemens P4 diffractometer fitted with graphite monochromator at 173 K. Structures were solved by direct methods and refined based on F^2 by use of SHELX package).[29] Crystallographic data were deposited with *Cambridge Crystallographic Center*. CCDC deposition numbers (see Supplementary Material) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.com.ac.uk/data_request/cif.

Methyl (1*SR,4RS*)-4-acetoxy-2,3-dimethyl-cyclohex-2-ene-1-carboxylate (*rac*-**6**)**.** To a solution of methyl-(1*SR,*4*RS*)-4-hydroxy-2,3-dimethyl-cyclohex-2-en-carboxylate (*rac*-**5**)[3,8,9] (7.0 g, 38 mmol) in THF (60 mL) were added Ac_2O (7.78 g, 7.2 mL, 76.2 mmol), NEt_3 (7.67 g, 10.5 mL, 76 mmol) and, dimethylamino pyridine (DMAP) (468 mg, 3.8 mmol) at 0° C. The mixture was stirred at 0° C for 2 h under an argon atmosphere. Then a saturated $NaHCO_3$ (100 mL) was added and the mixture was extracted three times with ether (3 x 50 mL). The combined organic layers were dried by filtration through cotton wool and evaporated. The obtained colorless oil was purified through silica gel chromatography [SiO_2 (80 g), petroleum ether/EtOAc 2 : 1] to give *rac*-**6** as a colorless oil (8.17 g, 95%). TLC (silica gel, petroleum ether/EtOAc 2 : 1): R_f 0.69. IR (solid, NaCl, ν_{max}, cm^{-1}): 2952, 2783, 1736s (C=O), 1435, 1372, 1337, 1243, 1193, 1164, 1123, 1076, 1019, 959, 921, 889, 876, 858. ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.66 [3H, s, H_3C-C(2 or 3)], 1.67 [3H, s, H_3C-C(3 or 2)], 1.80 – 1.90 (4H, m, -CH_2-CH_2-), 2.07 [3H, s, CH_3COO-C(4)], 3.0 [1H, m, H-C(1)], 3.71 [3H, s, H_3COOC-C(1)], 5.19 [1H, m, H-C(4)]. EI-MS (70 eV, 200° C): *m/z* (%) 226(11, M^+), 209 (4), 198 (6), 184 (38, [M - CH_2=CO]$^+$), 169 (10, [184 - CH_3]$^+$), 166 (16, [M - CH_3COOH]$^+$), 153 (10, [184 - OCH_3]$^+$), 124 (26, [184 - CH_3COOH]$^+$), 108 (12), 107 (100, [166 - $COOCH_3$]$^+$), 91 (17), 79 (10) 43 (32, [CH_3COO]$^+$). HRMS (EI): Calcd for ($C_{12}H_{18}O_4$) 226.12051. Found: 226.12037.

Methyl (1*S,4R*)-4-hydroxy-2,3-dimethylcyclohex-2-ene-1-carboxylate (**5**) and **methyl (1*R,4S*)-4-acetoxy-2,3-dimethylcyclohex-2-en-1-carboxylate** (*ent*-**6**). To a suspension of methyl-(1*SR*,4*RS*)-acetoxy-2,3-dimethyl-cyclohex-2-en-1-carboxylate (*rac*-**6**) (8.0 g, 35.4 mmol) in MeOH (10 mL) and aqueous 0.2 M pH 7 phosphate buffer [180 mL (from 11 g KH_2PO_4, 3.3 g KOH, 300 mL H_2O)] was added pig liver esterase [PLE, E.C. 3.1.1.1, Fluka (120 mg solved in 5 mL pH 7 phosphate buffer)] and stirred at 25° C for 48 h. During this time pH was kept constant by continuous addition of 1 N KOH *via* an automatic burette. The reaction mixture was extracted four times with ether (4 x 100 mL). The combined organic layers were washed with brine (50 mL) and dried by filtration through cotton wool. Evaporation of the solvent and drying in *vacuo* of an oil pump gave a colorless oil which was chromatographed on silica gel [SiO_2 (80 g), petroleum ether/EtOAc 2 : 1]. From a first fraction acetoxy derivative *ent*-**6** was obtained as oil which became solid on storage at 0° C (3.28 g, 41% related to *rac*-**6**). A second fraction containing alcohol **5** was eluted with petroleum ether/EtOAc (1 : 1). After evaporation of eluent and crystallization from ether/*n*-hexane alcohol **5** was obtained as colorless needles (2.152 g, 33% related *rac*-**6**, 66% related **6**, ee > 98%).

Ent-**6**: TLC (silica gel, petroleum ether/EtOAc 2 : 1): R_f 0.69. $[\alpha]_D^{20}$ -5.7° (c 1.03, CH_2Cl_2). IR (solid, NaCl, ν_{max}, cm^{-1}) 2952, 2783, 1732s (C=O), 1435, 1372, 1311, 1237, 1193, 1164, 1076, 1018, 958, 921, 889, 875, 857. ^{1}H

NMR (200 MHz, $CDCl_3$): δ_H 1.66 [3H, s, H_3C-C(2 or 3)], 1.68 [3H, s, H_3C-C(3 or 2)], 1.79 - 1.88 (4H, m, -CH_2-CH_2-), 2.07 [3H, s, H_3C-COO-C(4)], 3.01 [1H, m, H-C(1), 3.71 (3H, s, -CO_2CH_3), 5.19 [1H, m, H-C(4)]. EI-MS (70 eV, 200° C): *m/z* (%) 226 (20, M^+), 184 (42, [M - CH_2=CO]$^+$), 166 (8, [M - CH_3COOH]$^+$), 153 (9), 124 (20), 107 (100, [166 - CO_2CH_3]$^+$), 91 (14), 43 (24, $[CH_3O]^+$.

5: mp 92° C. TLC (silica gel, petroleum ether/EtOAc 1 : 1): R_f 0.51. $[\alpha]_D^{20}$ -17.8° (c 1.01 CH_2Cl_2). IR (solid, NaCl, ν_{max}, cm^{-1}): 3219, 2939, 2913, 1732s (C=O), 1452, 1434, 1341, 1315, 1292, 1188, 1087, 1014, 958, 863, 774, 736. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.65 [3H, s, H_3C-C(2 or 3)], 1.80 [3H, s, H_3C-C(3 or 2)], 1.96 (1H, s br, OH), 1.76 -1.83 (4H, m, -CH_2-CH_2-), 3.01 [1H, m, H-C(1)], 3.72 (3H, s, -CO_2CH_3), 3.96 [1H, m, H-C(4)]. EI MS (70 eV, 200° C): *m/z* (%) 184 (28, M^+), 169 (45, [M - CH_3]$^+$), 166 (30, [M - H_2O]$^+$), 124 (38), 107 (100, [166 - CO_2CH_3]$^+$), 91 (14), 43 (71, [M - CH_3O]$^+$). HRMS (EI): Calcd for ($C_{10}H_{16}O_3$) 184.10994. Found: 184.10907.

1´-Carbomethoxy-2´,3´-dimethyl-cyclohex-2´-en-4´-yl {(1´*S*,4´*R*,2*S*)-1-[(4"-methylphenyl)sulfonyl]}-pyrrolidine-2-carboxylate (**15**) and **(1´*R*,4´*S*,2*S*)-diastereomer** (**14**). Methyl-(1*SR*,4*RS*)-4-hydroxy-2,3-dimethyl-cyclohex-2-en-1-carboxylate (*rac*-**5**) (60 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (3.0 mL) and *N*-tosyl-*L*-proline hydrochloride (125 mg, 0.44 mmol), *N,N*-dimethyl-4-aminopyridine (DMAP) (3.7 mg, 0.03 mmol) and NEt_3 0.16 mL, 1.2 mmol) were added. The mixture was stirred under an argon atmosphere at rt for 5 h. Then the mixture was poured into a separating funnel and washed twice with 10% aqueous HCl (2 x 20 mL), saturated aqueous sodium bicarbonate (20 mL) and twice with water (2 x 20 mL). The organic layer was dried by filtration through cotton wool and the solvent was evaporated. The obtained residue was purified by chromatography on silica gel [SiO_2 (10 g), petroleum ether/EtOAc 1 : 1] to give the binary mixture of diastereomers **14**/**15** (128 mg, 90%). TLC (silica gel, petroleum ether/EtOAc 1 : 1): R_f 0.5. IR (solid, NaCl, ν_{max}, cm^{-1}): 2952, 2874, 1740s (C=O), 1731s (C=O), 1598, 1448, 1349, 1278, 1192, 1158, 1095, 1012, 66, 592, 548. ^{1}H NMR (360 MHz, $CDCl_3$, binary mixture of diastereomers **14**/**15**): δ_H 1.56 [3H, s, H_3C-C(3´)], 1.59, 1.69 [9H, s, 3 x H_3C-C(2´,2´,3´)], 1.64 - 1.97 [16H, m, H_2C(3,3), H_2C(4,4), H_2C(5´,5), H_2C(6´,6)], 2.33 (6H, s, 2 x H_3C-Ar), 2.93 [2H, s br, 2 x H-C(1´)], 3.19, 3.41 [4H, dm, 2 x H_2C(5)], ***3.62***, ***3.63*** [6H, ***2 s***, 2 x ***H_3C***OOC-C(1´)], 4.17 [2H, m 2 x HC-C(1)], 5.15 [2H, m 2 x H-C(4´)], 7.21 [4H, dd, 4 x H-Ar(*m*)], 7.67 [4H, d, 4 x H-Ar(*o*)]. ^{13}C NMR (360 MHz, $CDCl_3$, binary mixture of diastereomers **14**/**15**): δ_C 16.2,16.3 [2 H_3C(1´)], 17.8, 17.9 [2 H_3C(2´)], 21.5 (2 H_3C-Ar), 22.9, 23.0 [2 H_2C(6´)], 26.5, 26.6 [2 H_2C(5´)], 31.0, 31.1 [2 H_2C(3)], 47.4, 47.6 [2 HC(1´)], 48.4 [2 H_2C(5)], 51.8 (2 H_3COOC), 60.4, 60,6 [2 HC(2)], 72.3, 72.5 [2 HC(4´)], 127.5 [4 C(*o*-Ar)], 127.7, 127.9 [2 C(2´)], 129.6 [4 C(*m*-Ar)], 129.8, 130.0 [2 C(3´)], 135, 135.2 [2 C(SAr)], 143.4, 143.5 [2 C(*p*-Ar)], 172.1, 172.2 [2 RO_2C-C(2)], 174.8, 174.9 [2 MeO_2C-C(1´)]. Assignment of hydrogen and carbon signals was achieved by HH-NOESY-, HC-INEPT-, DEPT- and HSQC-experiments. EI-MS (70 eV, 200° C): *m/z* (%): 435 (7, M^+), 404 (weak, [M - OCH_3]$^+$), 376 (weak, [M - CO_2CH_3]$^+$), 280 (4, [M - tosyl]$^+$), 270 (100), 224 (100, [tosylprolinyl]$^+$), 183 (weak, [M - tosylprolinylcarbonyl]$^+$), 155 (21, [tosyl]$^+$), 107 (15), 91 (22). HRMS (EI): Calcd for ($C_{22}H_{29}NO_6S$) 435.17156. Found: 435.17139.

1´-Carbomethoxy-2´,3´-dimethylcyclohex-2´-en-4´-yl {(1´*S*,4´R,2*S*)-1-[(4´´-methylphenyl)-sulfonyl]}-pyrrolidine-2-carboxylate (**15**). Preparation of **15** from **5** (36.8 mg, 0.2 mmol) was performed according the procedure described for *rac*-**5**. Yield of **15** (77 mg, 88%). With exception of ^{1}H NMR spectroscopic data, IR, MS and HRMS for **15** were identical with those of **14**/**15**.

15: ^{1}H NMR (200 MHz $CDCl_3$) δ_H 1.71 [6H, s, H_3C-C(2´,3´)], 1.81 - 1.98 [4H, m, H_2C(5´), H_2C(6´)], 2.00 – 2.06 [4H, m, H_2-C(3), H_2-C(4)], 2.44 [3H, s, H_3C-Ar(*p*)], 3.03 [1H, m, HC(1´)], 3.35, 3.41 [2H, m, H_2C(5)], ***3.717*** [3H, ***s***, ***H_3C***-OOC-C(1´)], 4.32 [1H, m, HC(1)], 5.27 [1H, m, HC(4´)], 7.33 [2H, dd, 2 x H-Ar(*m*)], 7.78 [2H, d, 2 x H-Ar(*o*)].

14/**15**: ^{1} HNMR (200 MHz, $CDCl_3$) δ_H 1.71 [12H, 2s, 4 x H_3C-C(2´,2´,3´,3´)], 1.70 – 1.86 [8H, m, 4 x H_2C-C(5´,5´, 6´, 6´)], 1.86 – 2.06 [8H, m, 4 x H_2C-C(3, 3, 4, 4)], 2.44 [6H, s, H_3C-Ar(*p*)], 3.03 [2H, m, 2 x HC(1´)], 3.35, 3.53 [4H, 2m, 2 x H_2C(5)], ***3.715***, ***3.729*** [6H, ***2s***, 2 x ***H_3C***OOC-C(1´)], 4.28 [2H, m, 2 x HC(1)], 5.25 [2H, m, 2 x HC(4´)], 7.32 [4H, dd, 4 x H-Ar(*m*)], 7.78 [4H, d, 4 x H-Ar(*o*)].

Methyl (1*S*,2*S*)-2-[2-(dimethylamino)-2-oxoethyl]-2.3.-dimethyl-cyclohex-3-en-1-carboxylate (**2**) *was prepared according a procedure developed for* rac-**2** *during the course of the total synthesis of vitamin* B_{12}.[3,8,9] To a solution of methyl-(1*S*,4*R*)-4-hydroxy-2.3-dimethylcyclohex-2-en-1-carboxylate (**5**) (670 mg, 3.64 mmol) in *p*-xylene (12 mL) was added *N,N*-dimethylacetamide dimethylacetal (0.71 mL, 4.89 mmol, 1.34 eq). The mixture was refluxed in a Soxhlet apparatus filled with molecular sieves (4 Å) under an argon atmosphere for 3 h. The solvent was evaporated, the residue dried in *vacuo* of an oil pump and purified through silica gel chromatography [SiO_2 (85 g), ether]. *Cis* product ***2*** was obtained as colorless oil (580 mg, 64%) and a trace of *trans*-**2** as light yellow oil (10 mg, 1%). TLC (silica gel, ether): **2**: R_f 0.29; *trans*-**2**: R_f 0.37. **2**: $[\alpha]_D^{20}$ -57.4° (c 1.005, CH_2Cl_2). IR (solid, NaCl, ν_{max}, cm^{-1}): 2949, 2842, 1732s (C=O), 1652s (C=O), 1494, 1435, 1393, 1265, 1207, 1159, 1107, 1075, 1058. ^1H NMR (360 MHz, $CDCl_3$): δ_H 1.38 [3H, s, H_3C-C(2)], 1.67 [3H, s br , H_3-C(3)], 1.84 -1.98 [2H, m, H_2C(6)], 2.04 [2H, m, H_2C(5)], 2.42, 2.49, 2.70, 2.75 (2H, dd, AB system, -CH_2-CON=), 2.73 [1H, m, HC(1)], 2.92, 3.02 [6H, 2s, $N(CH_3)_2$], 3.66 (3H, s, $COOCH_3$), 5.42 [1H, m, HC(4)]. EI-MS (70 eV, 200° C): *m/z* (%) 253 (18, M^+), 238 (1, $[M - CH_3]^+$), 222 (6, $[M - OCH_3]^+$), 205 (6), 167 (2), 166 (2), 152 (7), 138 (8), 107 (26), 91 (7), 88 (36), 87 (100, $[CH_3\text{-}CON(CH_3)_2]^+$), 72 (29). HRMS (EI): Calcd for ($C_{14}H_{23}NO_3$) 253.16779. Found: 253.16729. *Trans*-**2**: IR (solid, NaCl, ν_{max}, cm^{-1}): 2949, 2842, 1728s (C=O), 1652s (C=O), 1488, 1452, 1435, 1397, 1253, 1215, 1152, 1132, 1102. ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.05 [3H, s, H_3C-C(2)], 1.60 [3H, s, H_3C-C(3)], 1.77 - 1.92 [2H, m, H_2C(6)], 1.96 – 2.18 [2H, m, H_2C(5)], 2.46, 2.73 (2H, dd, AB system, H_2C-CON=), 2.91, 3.03 [6H, 2 s, $N(CH_3)_2$], 3.43 – 3.50 [1H, m, HC(1)], 3.67 (3H, s, $COOCH_3$), 5.41 [1H, s br, HC(4)]. EI-MS (70 eV, 200° C): *m/z* (%) 253 (25, M^+), 238 (1), 22 (6), 205 (5), 167 (2), 166 (4), 152 (5), 138 (10), 107 (28), 91 (8), 88 (36), 87 (100, $[CH_3\text{-}CON(CH_3)_2]^+$), 72 (30).

Methyl {(1*S*,2*S*,5*S*)-1.5-dimethyl-3.7-dioxo-4-aza-6-oxabicyclo[3.3.0]oct-2-yl}-2-propionate (**3**) *was prepared according a modified procedure developed for* rac-**3** *during the course of total synthesis of vitamin* B_{12}.[3,9] Methyl-(1*S*,2*S*)-2-[2-(dimethylamino)-2-oxoethyl]-2.3-dimethyl-cyclohex-3-en-1-carboxylate (**2**) (1.0 g, 3.95 mmol) was solved in MeOH (110 mL) and reacted with a stream of O_3/O_2 at -80° C. Evaporation of MeOH, treatment with formic acid (80 mL) and H_2O_2 (40 mL, 35%) at 70° C followed by work up gave intermediate {(1S,2S,5S)-1.5-dimethyl-3.7-dioxo-4.6-dioxabicyclo[3.3.0]oct-2-yl-}-2-propoionate (**8**) (490 mg, 51%). TLC (silica gel, MeOH/EtOAc 3 : 1): R_f 0.6. ^1H NMR (360 MHz, $CDCl_3$): δ_H 1.22 [3H, s, H_3C-C(1)], 1.65 [3H, s, H_3C-C(5)], 1.89 [2H, m, AB system, -H_2C-C(2)], 2.59, 2.68 [2H, m, AB system, -H_2C-CO_2H], 2.78 [1H, dd, HC(2)], 2.79, 2.85 [2H, m, AB system, H_2C(8)]. MS (CI, negative, NH_3, 200° C): *m/z* (%) 483 (35, $[2M - H]^-$), 241 (100, $[M - H]^-$). MS (CI, positive, NH_3, 200° C): *m/z* (%) 260 (100, $[M + NH_4]^+$), 243 (3, $[M + H]^+$).

The product was reacted in the next synthetic step without further detailed characterization. *Bis*-lactone carboxylic acid **8** (600 mg, 2.5 mmol) was dissolved at 0° C in a saturated solution of NH_3 in MeOH (40 mL) and then stirred in a sealed flask at room temperature for 70 h. Gaseous HCl was bubbled through the reaction mixture for 1 h. The solvent was partially evaporated and precipitated NH_4Cl was filtered off. After complete removal of the solvent the residue was crystallized from CH_2Cl_2/acetone/*n*-hexane to give lactone-lactam methylester **3** as colorless crystals (370 mg, 7%).

In an alternative procedure intermediate **8** (256 mg, 1.01 mmol) was reacted with [1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP)] (1.2 g, 2.71 mmol), NEt_3 (3 mL, 21.64 mmol) and MeOH (17 mL, 0.42 mmol) in THF (15 mL) at rt for 24 h to form methyl ester **3**. After workup, chromatography on silica gel [SiO_2 (25 g), EtOAc] and crystallization from CH_2Cl_2/acetone/*n*-hexane **3** was obtained as colorless crystals (165 mg, 64%). mp 137° C, (ref.[21] 137 – 138° C). TLC (silica gel, EtOAc): R_f 0.45. $[\alpha]_D^{20}$ +55° (c 1.05, $CHCl_3$),(ref.[21] $[\alpha]_D^{23}$ +55°). IR (solid, KBr, ν_{max}, cm^{-1}): 3434, 3203, 3110, 2952, 2910, 2893, 1780s (C=O), 1731s (C=O), 1709s (C=O), 1457, 1434, 1392, 1352, 1259, 1236, 1198, 1179, 1069, 921. ^1H NMR (600 MHz, $CDCl_3$): δ_H 1.2 [3H, s, H_3C-C(1)], 1.59 [3H, s, H_3C-C(5)], 1.81, 1.96 [2H, 2m, AB system, -H_2C-C(2)],

2.41 [1H, dd, HC(2)], 2.56, 2.81 [2H, 2d, AB system, $H_2C(8)$], 2.63, 2.78 (2H, 2m, AB system, H_2C-COOMe), 3.7 (3H, $COOCH_3$), 6.32 (1H, s, NH). EI MS (70 eV, 200° C): *m/z* (%) 255 (13, M^+), 224 (20, $[M - OCH_3]^+$), 196 (12, $[M - CO_2CH_3]^+$), 169 (20, $[M - CH_2CH_2CO_2CH_3]^+$), 124 (100, 169 – $CO_2]^+$), 110 (10), 107 (42), 90 (35), 77 (37), 52 (32), 39 (24). HRMS (EI): Calcd for ($C_{12}H_{17}NO_5$) 255.11067. Found: 255.11108.

Methyl {(1*S*,2*S*,5*S*)-1.5-dimethyl-7-oxo-3-thiooxo-4-aza-6-oxabicyclo[3.3.0]oct-2-yl}-2-propionate (**10**)**.** To a solution of methyl-{(1*S*,2*S*,5*S*)-1.5-dimethyl-3.7-dioxo-4-aza-6-oxabicyclo[3.3.0]oct-2-yl}-2-propionate (**3**) (181 mg, 0.71 mmol) in THF (20 mL) was added Lawesson´s reagent (380 mg, 0.94 mmol, 1.3 eq) and the reaction mixture was refluxed under an Ar atmosphere for 1 h. The solvent was evaporated and the residue was purified through chromatography on silica gel laminated with a slice of 2 cm aluminium oxide [Alox N II – III (2 g), SiO_2 (7 g), CH_2Cl_2/EtOAc 1 : 1]. After crystallization from EtOAc/*n*-hexane the first fraction gave colorless crystals of thiolactam **10** (161 mg, 84%). From a second fraction 2-*epi*-**10** was obtained (16 mg, 8.4%). **10**: mp 136 – 137° C (ref.[21] 138 – 139° C). TLC (silica gel, CH_2Cl_2/EtOAc 1 : 1): R_f 0.6. $[\alpha]_D^{20}$ +118° (c 1.00 $CHCl_3$), (ref.[21] $[\alpha]_D^{23}$ +118°). CD: Θ (λ) 1415 (267 nm), (c 9.40 x 10^{-5} M, MeOH). UV/Vis [$CHCl_3$, λ, nm, (ε, $Lmol^{-1}cm^{-1}$)]: 269 (14008). IR (solid, NaCl, ν_{max}, cm^{-1}): 3285, 2982, 2952, 1779s (C=O), 1732s (C=O), 1504, 1495s (C=S), 1441, 1385, 1292, 1260, 1203, 1175. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.18 [3H, s, H_3C-C(1)], 1.61 [3H, s, H_3C-C(5)], 1.88, 2.20 [2H, 2m, AB system, -H_2C-C(2)], 2.70 [1H, dd, HC(2)], 2.56, 2.88 [2H, 2d, AB system $H_2C(8)$], 2.79 (2H, m, -H_2C-COOMe), 3.73 (3H, s, -OCH_3), 8.14 (1H, s, NH). EI-MS (70 eV, 200°C): *m/z* (%) 271 (100, M^+), 240 (34, $[M - OCH_3]^+$), 212 (50, $[M - CO_2CH_3]^+$), 198 (12, $[M - CH_2CO_2CH_3]^+$), 185 (18, $[M - CH_2CH_2CO_2CH_3]^+$), 180 (20), 160 (20), 142 (100) 140 (73), 126 (20), 11 (30), 100 (10), 81 (9). HRMS (EI): Calcd for ($C_{12}H_{17}NO_4S$) 271.08783. Found: 271.08742.

Methyl {(1*S*,2*S*,5*S*,3*Z*)-3-(2-*tert*-butoxy-2-oxoethylidene)-1.5-dimethyl-7-oxo-4-aza-6-oxa-bicyclo[3.3.0]oct-2-yl}-2-propionate (**12**)**.** To a solution of methyl-{(1*S*,2*S*,5*S*)-1.5-dimethyl-7-oxo-3-thiooxo-4-aza-6-oxa-bicyclo-[3.3.0]oct-2-yl}-2-propionate (**10**) (108 mg, 0.4 mmol) in MeCN (6 mL) were added allyl *tert*-butyl bromomalonate (**11**) (181 mg, 0.65 mmol, 1.63 eq) and DBU (105 mg, 0.69 mmol, 1.73 eq). The reaction mixture was stirred at 0° C under an Ar atmosphere for 1 h. Progress of the coupling reaction was monitored by TLC (silica gel, CH_2Cl_2/EtOAc 1 : 1). The reaction mixture was worked up with CH_2Cl_2 (15 mL) and ice cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried by filtration through cotton wool, the solvent evaporated and the residue dried in *vacuo* of an oil pump. To achieve the sulfide contraction step the crude coupling product was heated in $P(OEt)_3$ (5 mL) at 80° C under an Ar atmosphere for 18 h. $P(OEt)_3$ was removed by bulb to bulb distillation in *vacuo* of an oil pump and the residue was purified by chromatography on silica gel laminated with a slice of 2 cm aluminium oxide [Alox N II – III (2 g), SiO_2 (7 g), CH_2Cl_2/EtOAc 8.5 : 1]. To a solution of the crude diester in THF (1.5 mL) was added $Pd(PPh_3)_4$ (90 mg) and piperidine (0.5 mL, 5 mmol) and the mixture was stirred at rt under an Ar atmosphere for 6 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL), HOAc (0.5 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried by filtration through cotton wool and evaporated. The crude product was purified by chromatography on silica gel laminated with a slice of 2 cm aluminium oxide [Alox N II – III (2 g), SiO_2 (7 g), CH_2Cl_2/EtOAc 8.5 : 1]. Evaporation of the eluent and crystallization of the residue from ether/*n*-hexane gave colorless crystals of **12** (84.8 mg, 60%). mp 164.5° C. TLC (silica gel, CH_2Cl_2/EtOAc 8.5 : 1): R_f 0.46. CD: Θ (λ) 7944 (265 nm), (c 2.86 x 10^{-5} M, MeOH). UV/Vis [$CHCl_3$, λ, nm (ε, $Lmol^{-1}cm^{-1}$)]: 269 (20030). IR (solid, KBr, ν_{max}, cm^{-1}): 3369, 2977, 2929, 1770s (C=O), 1738s (C=O), 1673s (C=O), 1617s (C=C), 1436, 1392, 1367, 1232, 1219, 1143, 1068, 916. ^{1}H NMR (600 MHz), $CDCl_3$): δ_H 1.13 [3H, s, H_3C-C(1)], 1.45 [9H, s, -$C(CH_3)_3$], 1.59 [3H, s, H_3C-C(5)], 1.9 [2H, m, AB system, -H_2C-C(2)], 2.5 (2H, m, AB system, -H_2C-CO_2Me), 2.64 [1H, dt, HC(2)], 2.51, 2.75 [2H, 2d, AB system, $H_2C(8)$], 3.75 (3H, s, -OCH_3), 4.61 (1H, d, =CH-CO_2*t*Bu), 8.41 (1H,

m, NH). ^{13}C NMR (360 MHz, $CDCl_3$): δ_C 15.2 [H_3C-C(1)], 20.9 [H_3C-C(5)], 22.2 [-H_2C-C(2)], 28.5 [-C(CH_3)$_3$], 32.3 (-H_2C-CO_2Me), 41.9 [C(8)], 48.9 [C(1)], 49.2 [C(2)], 52.0 (-CO_2CH_3), 79.3 [-O*C*(CH_3)$_3$], 84 (=*C*H-CO_2*t*Bu), 104.0 [C(5)], 162.3 [C(3)], 169.5 (=CH-*C*O_2), 172.7 (-*C*O_2Me), 173.1 [C(7)]. EI-MS (70 eV, 200° C): *m/z* (%) 353 (20 M^+), 297 (40), 280 (44, [M - O*t*Bu]$^+$), 288 (40, [M – CO_2*t*Bu]$^+$), 238 (100, [$C_6H_{11}O_2$]$^+$), 224 (32), 211 (36), 168 (40), 166 (60), 148 (28), 57 (16), 43 (12). HRMS (EI): Calcd for ($C_{18}H_{27}NO_6$) 353.18384. Found: 353.18380.

Methyl [(2*RS*,3*SR*,4*SR*,5*Z*)-5-(2´-*tert*-butoxy-2´-oxoethylidene)-2-cyano-4-(3"-methoxy-3"-oxoprop-1"-yl)-2.3-dimethylpyrolidin-3-yl]acetate (*rac*-**17a**) **and (2*SR*,3*SR*,4*SR*,5*Z*)-diastereomer** (*rac*-**17b**). Methyl {(1*RS*,2*RS*,5*RS*3*Z*)-3-(2-*tert*-butoxy-2-oxo-ethylidene)-1.5-dimethyl-7-oxo-4-aza-6-oxa-bicyclo[3.3.0]oct-2-yl}-2-propionate (*rac*-**12**) (7.6 mg, 57 µmol) and KCN (20 mg, 0.12 mmol, 2 eq) were dissolved in MeOH (1.2 mL) and stirred at rt under an Ar atmosphere for 20 h. After evaporation of part of the solvent 2 M aqueous Na_2HPO_4 (3 mL) was added and the pH value was adjusted to 2 - 3 by addition of concentrated H_3PO_4. To the mixture was added NaCl until saturation and then it was extracted four times with EtOAc (4 x 10 mL). The combined organic layers were dried by filtration through cotton wool and evaporated. The residue was chromatographed on silica gel [SiO_2 (6g), CH_2Cl_2/EtOAc 8.5 : 1]. The first eluted fraction gave re-isolated educt *rac*-**12** (8 mg, 40%). Further elution with MeOH yielded a diastreomeric mixture of carboxylic acids *rac*-**16a,b** (12 mg, 56%, 93% related reacted *rac*-**12**). TLC (silica gel, CH_2Cl_2/EtOAc/MeOH 8.5 : 1 : 1): R_f 0.38. IR (solid, KBr, ν_{max}, cm^{-1}): 3436, 3369, 2976, 2992, 2353s (CN), 1729s (C=O), 1667s (C=O), 1621, 1455, 1390, 1364, 1290, 1232, 1150, 1061. ^{1}H NMR (200 MHz, CD_3OD, 8 : 2 binary mixture of diastereomers *rac*-**16a,b**): δ_H 1.26, 1.38 [6H, 2s, 2 x H_3C-C(3)], 1.48 [18H, s, -C(CH_3)$_3$], 1.60, 1.70 [6H, 2s, 2 x H_3C-C(3)], 1.85 – 2.08 [4H, m, 2 x H_2C-C(4)], 2.32 – 2.64 (4H, m, 2 x -H_2C-CO_2Me), 2.39 - 2.64 (4H, m, AB system, -H_2C-CO_2H), 2.92 [2H, m, 2 x HC(4)], 3.69, 3.70 (6H, 2s, CO_2CH_3), 4.52 (2H, d, =CHCO_2*t*Bu), 8.10 (2H, s, 2 x NH). MS (ESI positive): *m/z* 381 [M + H]$^+$, 403 [M + Na]$^+$, 419 [M + K]$^+$. Carboxylic acid *rac*-**16a,b** was reacted in the next step without further detailed characterization. To an ice cold solution of the acid (12 mg, 31.3 µmol) in MeOH (1.0 mL) was added CH_2N_2 in ether (0.2 mL, 1.0 M solution) and kept at rt for 10 min. The solvent was evaporated, the residue dried in *vacuo* of an oil pump and purified by chromatography on silica gel [SiO_2 (8 g), CH_2Cl_2/EtOAc 10 : 1]. The diastereomeric mixture of methyl ester *rac*-**17a,b** was obtained as colorless oil (8.5 mg, 68% rel *rac*-**16a,b**). TLC (silica gel, CH_2Cl_2/EtOAc): R_f 0.63. IR (solid, KBr, ν_{max}, cm^{-1}): 3336, 2973, 2955, 1734s (C=O), 1730s (C=O), 1664s (C=O), 1611s (C=C), 1439, 1363, 1269, 1252, 1208, 1139, 1044, 1009. ^{1}H NMR (360 MHz, $CDCl_3$, 8 : 2 binary mixture of diastereomers): δ_H 1.35, 1.58, 1.65, 1.66 [12H, 4s, H_3C-C(2,2,3,3)], 1.46 [18H, s, 2 x -C(CH_3)$_3$], 1.88 - 2.05 [4H, m, 2 x -H_2C-C(4)], 2.32 - 2.46 [4H, m, 2 x -H_2C-C(3)], 2.39 - 2.64 (4H, m, 2 x -H_2C-CO_2Me), 2.75 [2H, dd, 2 x HC(4)], 3.69, 3.70 (12H, 2s, 4 x -CO_2CH_3), 4.55, 4.56 (2H, 2s, 2 x =CHCO_2*t*Bu), 8.01, 8.10 (2H, 2s, 2 x NH). ^{13}C NMR (90 MHz, $CDCl_3$): δ_C 17.4 [H_3C-C(3)], 22.2 [H_3C-C(2)], 23.4 [-H_2C-C(4)], 28.7 [-C(*C*H_3)$_3$], 32.8 [-CH_2-*C*H_2-CO_2Me], 39.2 [-H_2C-C(3)], 47.8 [C(3)], 49.3 [HC(4)], 51.9 [-OCH_3 propionate], 51.97 [-OCH_3 acetate], 63.3 [C(5)], 79.2 [-O*C*(CH_3)$_3$], 84.1 [=*C*HCO_2*t*Bu], 121 [CN], 162.5 [C(5)], 170 [-CO_2*t*Bu], 171 [-CO_2Me acetate], 173 [-CO_2Me propionate]. EI-MS (70 eV, 200° C): *m/z* (%) 394 (10, M^+), 367 (5, [M - HCN]$^+$), 338 (20, [M – C_4H_8]$^+$), 321 (18, [M - O*t*Bu]$^+$), 307 (11), 294 (10, [367 - O*t*Bu]$^+$), 280 (6), 265 (100, [338 – $CH_2CO_2CH_3$]$^+$), 252 (23), 238 (50), 221 (10), 220 (15), 179 (55), 152 (12), 138 (5). HRMS (EI): Calcd for ($C_{20}H_{30}N_2O_6$) 394.039. Found: 394.21020.

Cyanomethyl [(2*RS*,3*RS*,4*SR*,5*Z*))-5-(2´-tert-butoxy-2´-oxoethylidene)-2-cyano-4-(3"-methoxy-3"-oxoprop-1-yl)-2.3-dimethylpyrrolidin-3-yl]acetate (*rac*-**18a**) and **(2*SR*,3*SR*,4*SR*,5*Z*)-diastereomer** (*rac*-**18b**). To an ice cold solution of carboxylic acid *rac*-**16a,b** (15 mg, 39 µmol) in CH_2Cl_2 (0.5 mL) were added NEt_3 (15 µL, ca. 2 eq) and chloroacetonitrile (6 µL, ca. 2 eq.). The mixture was stirred at rt under an Ar atmosphere for 18 h. The solvent was evaporated, the residue dried *in vacuo* of an oil pump and purified by chromatography on slica gel [SiO_2 (8 g), CH_2Cl_2/EtOAc 10 : 1]. The binary diastereomeric mixture of cyanomethyl ester *rac*-**18a,b** was obtained as colorless oil (10 mg, 60%). TLC (silica gel, CH_2Cl_2/EtOAc 10 : 1): R_f 0.36. IR (solid, KBr, ν_{max}, cm^{-1}): 3339, 2968,

2929, 2354s (CN), 1736s (C=O), 1730s (C=O), 1666s (C=O), 1613s (C=C), 1437, 1366, 1262, 1140, 1005. ^{1}H NMR (360 MHz, $CDCl_3$, 8 : 2 binary mixture of diastereomers): δ_H 1.39 [6H, s, 2 x H_3C-C(3)], 1.47 [18 H, s, 2 x –$C(CH_3)_3$], 1.59 [6H, s, 2 x H_3C-C(2)], 1.88 – 2.05 [4H, m, 2 x –H_2C-C(4)], 2.41 – 2.66 (4H, m, 2 x –H_2C-CO_2Me), 2.42 – 2.58 [4H, m, 2 x -H_2C-C(3)], 2.73 [2H, m, 2 x HC(4)], 3.70 (6H, s, 2 x CO_2CH_3), 4.58 (2H, s, 2 x =$CHCO_2t$Bu), 4.49-4.85 (4H, dd 2 x –H_2C-CN), 8.11 (2H, s, 2 x NH). EI-MS (70 eV, 141^o C): *m/z* (%) 419 (M^+), 363 (20, [M – C_4H_8]$^+$), 346 (23, [M - O*t*Bu]$^+$), 288 (8), 277 (12, [M – HCN – CH_2CO_2tBu]$^+$), 265 (100), 251 (16), 238 (27), 221 (7), 179 (100), 166 (10), 152 (16), 138 (16). HRMS (EI): Calcd for ($C_{21}H_{29}N_3O_6$) 419.20564. Found: 419.20521.

Acknowledgements

We thank Dr. Thomas Dülcks, Dipl.-Ing. Dorit Kemken, Dipl.-Ing. Johannes Stelten (Institute of Organic and Analytical Chemistry, Laboratory Prof. Dr. Peter Spiteller) for numerous mass spectrometry and NMR spectroscopy measurements. We are indebted to Dr. Klaus Rischka (IFAM Fraunhofer Institute, Bremen) who recorded UV/Vis spectra and Dr. Helmut Rosemeyer (Department of Chemistry, University of Osnabrück) CD spectra. This work was supported by Deutsche Forschungsgemeinschaft. Dr. Doan Duy Tien was supported with a scholarship by the Vietnamese Government (Project Program 322 Committee). We thank Prof. Dr. Albert Eschenmoser and Dr. Engelbert Zass for discussions.

Supplementary Material

Supplementary data associated with this article is available in the Supplementary Material.

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20. To distinguish in schemes a compound represented by a formula depicting its absolute configuration from its enantiomer and from its racemic mixture, we use the suggestion made by Quinkert *et al*.[30] In brief: an enantiopure compound, whose configurational formula has been depicted, is represented also by its arabic numeral **N**. If its enantiomer should be mentioned only the arabical numeral prefixed by ent is used, thus leading to ent-**N**. For racemic mixtures of **N** prefixed rac-**N** is used.
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