

Ethyl 4,4-dimethyl pyroglutamate (DMPG): a chiral auxiliary in cyclopropanation and carbonyl group activator

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This manuscript is dedicated to Prof. Julio Alvarez-Builla on occasion of his 65th birthday

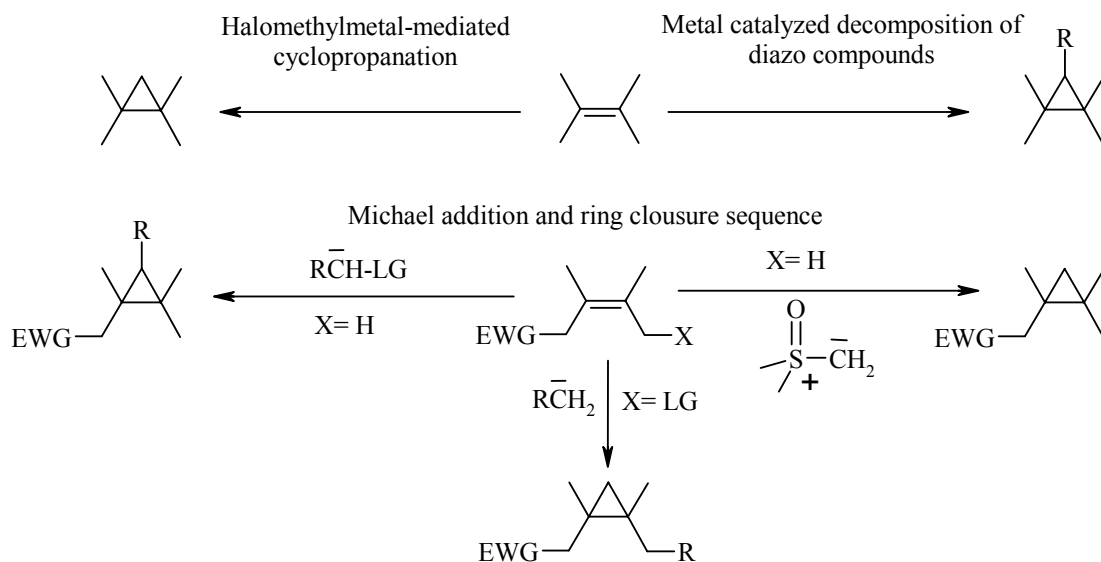
Abstract

Reaction of ethyl (*S*)-*N*-*trans*-2-butenoyl-4,4-dimethyl pyroglutamate with ethyl (dimethylsulfuranylidene) acetate (EDSA) or with Trost's ylide gave rise to stereoselective cyclopropanation, promoted by the chiral auxiliary (*S*)-ethyl 4,4-dimethyl pyroglutamate (DMPG), which can easily be removed from the highly functionalised cyclopropanated products using various nucleophiles.

Keywords: (*S*)-Ethyl 4,4-dimethyl pyroglutamate (DMPG), nucleophilic stereoselective cyclopropanation

Introduction

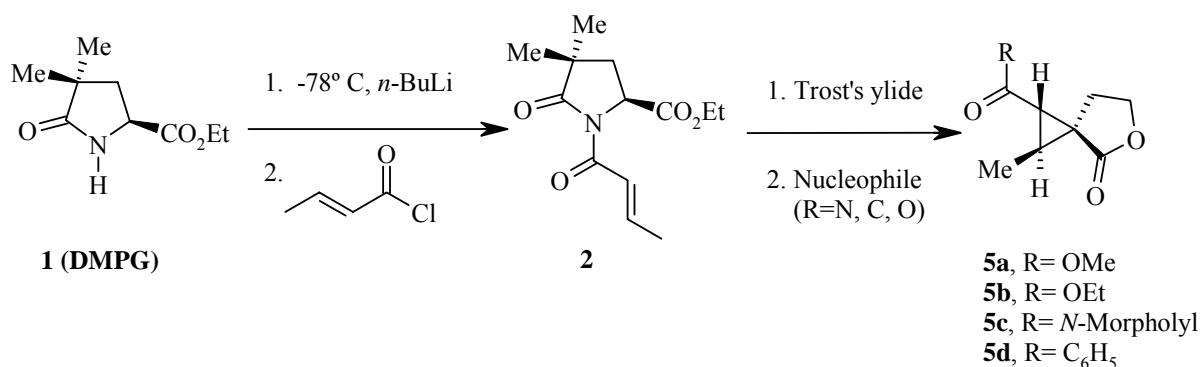
The cyclopropane ring is found in natural products such as terpenes, pheromones and some amino acids.¹ General methods for the cyclopropanation of olefins include the Simmons-Smith reaction² and reaction with diazomethane/palladium acetate³ and diazoesters.⁴ Corey also demonstrated that the addition of dimethyl sulfoxonim methylide to α,β -unsaturated ketones affords the corresponding cyclopropyl ketones.⁵ This method, which involves sequential Michael addition followed by intramolecular displacement of dimethyl sulfoxide, has become widely appreciated as the most general procedure for cyclopropanation of activated, electron deficient alkenes (Scheme 1). Furthermore, other sulfur⁶ or phosphorus ylides⁷ have been successfully employed in cyclopropanations using various types of Michael acceptor.



Scheme 1

Although there are a variety of stereoselective methods for the cyclopropanation of electron-rich olefins,⁸ the number of reports focused on the stereoselective cyclopropanation of enones and related α,β -unsaturated compounds is quite limited. Previous examples included stereoselective cyclopropanation of cyclic enones⁹ and optically active acyclic enolates or enones derived from glyceraldehyde acetonide (Garner's aldehyde).¹⁰ Hanessian et al have reported an efficient asymmetric cyclopropanation using chloroallyl phosphonamides.¹¹ More recently an enantioselective cyclopropanation of *N*-enoyloxazolidinones¹² mediated by Lewis acids has been reported and Barluenga¹³ has described the diastereo- and enantioselective cyclopropanation of alkenyl oxazolines with chromium Fischer carbene complexes. Our contributions in the field include the diastereoselective cyclopropanation of cyclic and acyclic enones with ethyl dimethylsulfonium acetate bromide,¹⁴ and the stereoselective cyclopropanation of enantiomerically pure dihydroxycyclopentenones for the enantioselective synthesis of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid.¹⁵ In the light of our findings with (*S*)-ethyl 4,4-dimethyl pyrroglutamate **1** (DMPG)¹⁶ as an efficient chiral auxiliary in stereoselective aldol condensations¹⁷ and asymmetric Michael addition¹⁸ reactions, it was of interest to explore the behaviour of *N*-enoyl substrates incorporating DMPG towards an stereoselective cyclopropanation reaction. The DMPG group will not only activate the *N*-enoyl carbonyl group for the cyclopropanation reaction but also it will provide a means for further functionalization when reacted with an appropriate nucleophile. This synthetic approach will deliver cyclopropyl containing compounds **5** in an enantiomerically pure form as compared with our racemic cyclopropanation of acyclic α,β -unsaturated ketones.¹⁴ Additionally since the removal of the chiral auxiliary requires the reaction of **2** with a nucleophile, this single synthetic approach can deliver cyclopropanated products as those arising from esters, amides or ketones **5a-d** from a

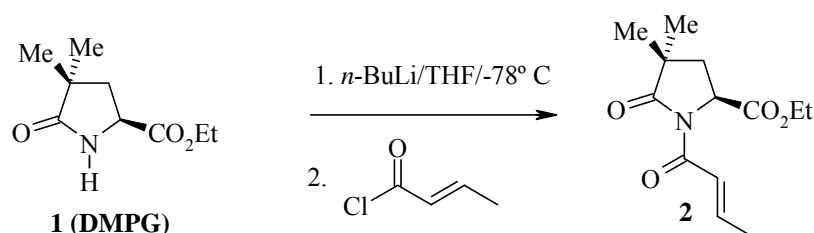
single substrate. (Scheme 2)



Scheme 2

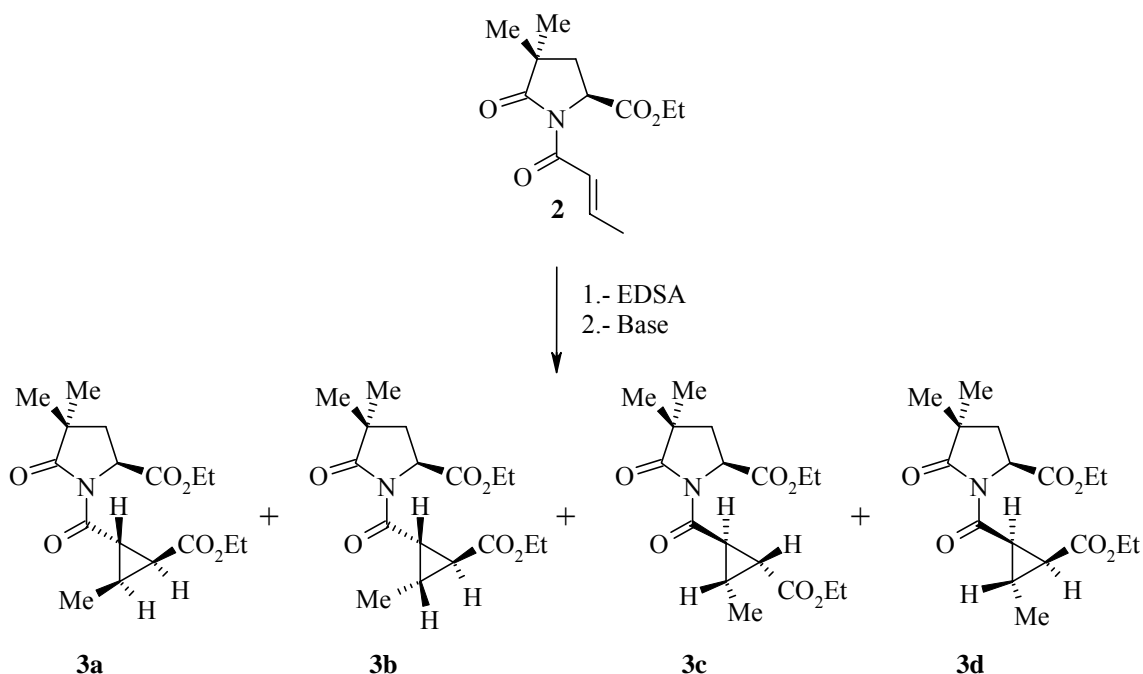
Results and Discussion

In this communication, we report our results concerning the successful reaction of ethyl (*S*)-*N*-*trans*-2-butenoyl-4,4-dimethyl pyroglutamate **2** with sulfonium ylides, leading to cyclopropanes with a high degree of diastereoselectivity, and the subsequent chemoselective removal of the auxiliary, using both heteronucleophiles and C-nucleophiles. The pyroglutamate derivative **2** used in this study was obtained in an 80% yield by treatment of **1** with *n*-butyllithium followed by reaction with crotonyl chloride.^{16,18} The dimethylsulfonium acetate bromide (EDSA)¹⁹ and *S,S*-dimethyl-*S*-(2-oxotetrahydro-3-furyl)sulfonium fluoroborate²⁰ (Trost's salt) used in this study were prepared following literature procedures.



Scheme 3

Based on our previous studies with enones and ethyl dimethylsulfonium acetate bromide,^{14,15} 1,8-diazabicyclo-[5,4,0]undec-7-ene (DBU) was chosen as base to generate *in situ* ethyl (dimethylsulfuranylidene) acetate (EDSA) from the sulfonium salt. In toluene at room temperature **2** reacted slowly with EDSA giving, after 90 h, a mixture of cyclopropanes **3a-d**²¹ in a 63% yield. The yield of the cyclopropanation was improved to 87% by use of a 1:1 mixture of THF/CH₃CN, in only 36 h at room temperature (Scheme 4).



Scheme 4

Table 1 shows the stereoselectivity of the cyclopropanation under the above conditions. Changes in solvent, temperature and reaction time did not improve the stereoselectivity of the reaction.

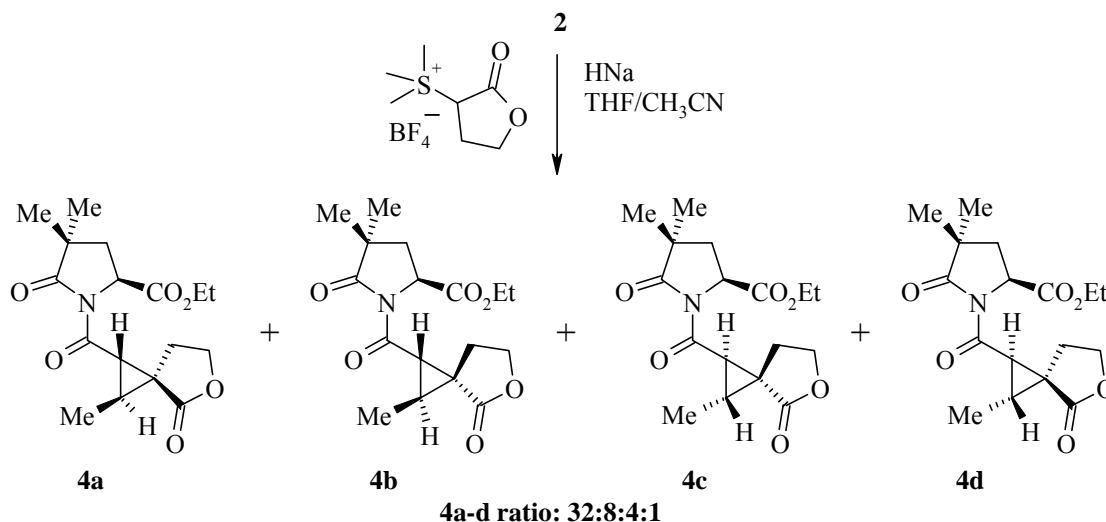
Table 1. Cyclopropanation with EDSA

Entry	Solvent	Conditions	Yield (Prod. ratio ^a)		
			3a+3b	3c	3d
1 ^b	Toluene	rt, 90 h	18% (11)	45% (27)	2% (1)
2	Toluene	40 °C, 24 h	Decomposition		
3 ^b	MeCN/THF (1:1)	rt, 36 h	42% (2)	21% (1)	20% (1)
4	MeCN/THF (1:2)	5 °C, 24 h	Low conversion		
5	MeCN/THF (1:2)	rt, 24 h	25% (2)	25% (2)	11% (1)
6	Toluene/MeCN (8:1)	rt, 24 h	25% (5)	24% (5)	5% (1)
7	Toluene/MeCN (1:1)	rt, 24 h	18% (1)	20% (1)	18% (1)
8	Toluene/THF (8:1)	rt, 24 h	22% (1)	20% (1)	22% (1)
9	Toluene/THF/MeCN (2:1:1)	rt, 24 h	15% (2)	15% (2)	6% (1)

^aData obtained by NP-HPLC. ^b Entry 1: ratio **3a/3b** (6:1); Entry 3: ratio **3a/3b** (3:2) (ratio obtained by chiral NP-HPLC).

Reaction of **2** with the ylide generated from Trost's salt (HNa/THF/CH₃CN) afforded the expected cyclopropanes in yields ranging from 72% to 91%, depending upon the excess of the

salt used, the yield being optimal when the reaction was carried out with 1.5 equiv. Analysis of the reaction product showed that it was a mixture of four components. The two major cyclopropanes **4a** and **4b** represent an 80% yield and could be separated by chromatography (4:1 ratio) while the mixture **4c/4d** (11%) was analyzed by NMR; the ^1H spectrum reveals a 4:1 ratio of products in the mixture (Scheme 5).



Scheme 5

The stereochemistry of cyclopropanes **3** and **4** was determined by NMR spectroscopy. The initial step was the assignment of resonances through a combination of ^1H , gCOSY and gHSQC experiments. The relative configuration of isomers **3** was deduced from ^3JHH analysis. For instance, the relevant coupling constants for **3a** are $^3\text{J}_{7-8} = 4.7$ Hz, $^3\text{J}_{7-9} = 5.0$ Hz and $^3\text{J}_{8-9} = 9.5$ Hz. Since it is well established that for cyclopropanes $^3\text{J}_{\text{cis}} > ^3\text{J}_{\text{trans}}$, these values indicate that H7 is *trans* to both H8 and H9. This assignment was confirmed through NOE data, as shown in Figure 1.

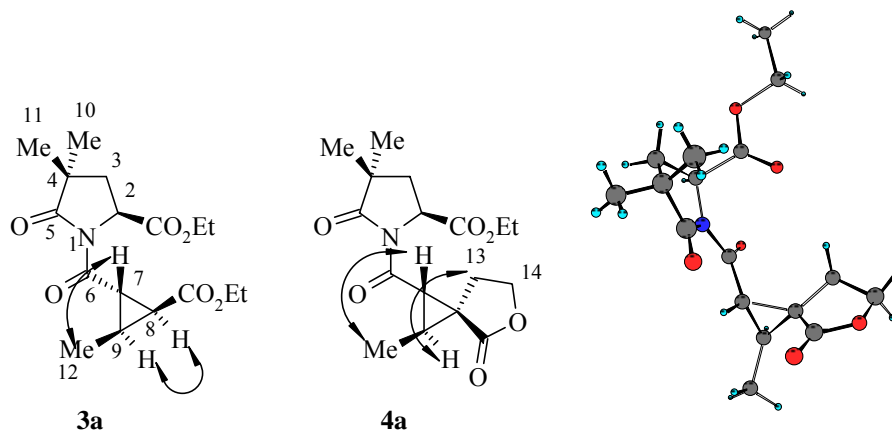
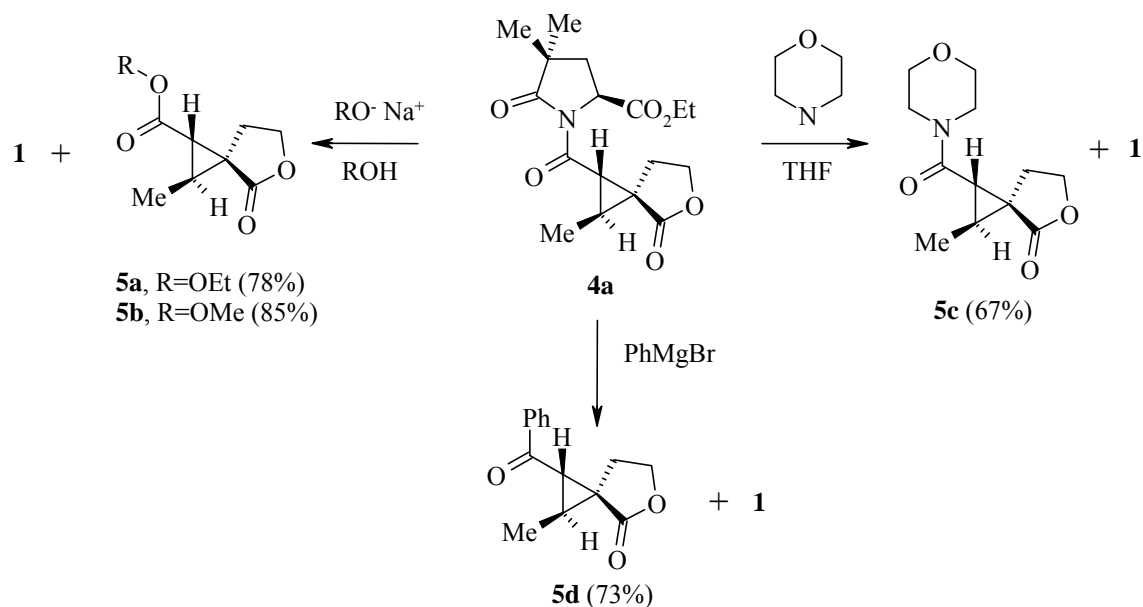


Figure 1. Representative NOEs for major isomers **3a** and **4a** (left) and X-ray structure of **4a** (right).

Similar analyses were carried out for compounds **3b** and **3c**. Furthermore, the relative configuration of cyclopropanes **4a** and **4b** was elucidated through 1D and 2D-NOESY experiments. Strong NOEs between H7 and the methyl protons were observed for both isomers. On the other hand, the methylene protons of the lactone ring showed a NOE to H9 for **4a** and to the methyl protons for **4b**. The observed NOEs reveal that H7 is *cis* to the methyl group in both isomers and the difference between them lies in the configuration at C8 (Figure 1). Chemical shifts, $J_{7,9}$ value and NOE effects for **4c** are very similar to those found for **4a**, reflecting that both isomers have the same relative configuration in the cyclopropane ring. Similarly, **4b** and **4d** also present the same configuration in the ring. The absolute configuration of these derivatives was established by X-ray analysis of **4a**²² (Figure 1) confirming the anticipated result from the NMR structural analysis.

These results contrast with our previous studies where EDSA reacted with enones but showed a lack of reactivity towards α,β -unsaturated aldehydes, esters, nitriles and amides.¹⁴ Furthermore, although the stereoselectivity in the reaction with EDSA is low, DMPG promotes cyclopropanation in excellent yields and with a good level of diastereoselection under non-chelation control conditions of the substrate^{9,12} when Trost's salt is used as the sulfonium ylide precursor. The origin of this diastereoselectivity presumably involves a dominant reactive rotamer for **2** with predominant attack of the ylide at the β -carbon from the opposite face to the pyroglutamate carboxylate group. This simple model, however, does not entirely unravel the selectivity observed with the Trost's salt when compared with EDSA. The question remains whether ylides themselves or the different bases used in the two reactions (DBU and HNa) are responsible for the different diastereoselectivity observed. Unfortunately, our attempts to study the role of the base on the stereoselectivity failed due to the lack of reactivity of Trost's salt in the presence of DBU and the poor yield of cyclopropanated products obtained when HNa was used to generate the EDSA ylide. We have recently shown that DMPG can be selectively removed by chemoselective nucleophilic displacement on *N*-acyl DMPG derivatives, with O-, N-, and C-nucleophiles.²³

The removal of the DMPG from the cyclopropane **4a** presents an extra challenge, in terms of nucleophile selectivity, with the introduction of the lactone carbonyl. We have found that the DMPG could be chemoselectively removed from **4a** using alkoxides, amines or Grignard reagents, giving the corresponding tetrasubstituted cyclopropanes **5a-d** in good yields and without erosion of their stereochemical integrity (Scheme 6). In summary, we have shown that the cyclopropanation reaction of (*S*)-*N*-*trans*-2-butenoyl-4,4-dimethyl pyroglutamate with sulfonium ylides proceeds in high yields and with diastereocontrol of the stereogenic centers of the cyclopropane ring. Moreover, the chiral auxiliary (DMPG) can be chemoselectively removed from the cyclopropanated compounds using heteronucleophiles and Grignard reagents, permitting recovery of DMPG and formation of highly functionalised cyclopropanes.



Scheme 6

Experimental Section

General. All common reagents and solvents were obtained from commercial suppliers and used without any further purification unless otherwise indicated. NP-HPLC analytical work was recorded at Series 1100 Liquid Chromatography / Mass Selective Detector LC/MSD (Agilent, Waldbronn, Germany) driven by ChemStation software. NP-HPLC semi-preparative work was recorded at Waters Delta Prep 4000 Liquid Chromatography / Photodiode Array Detector (Waters, USA) controlled through Mass Lynx software. NP-HPLC preparative work was recorded at Hipersep Lab LC 50-80 system/variable ultraviolet and Refractive Index Detectors (Novasep, France) driven by ChromSoftLab central system (iFIX™ software). Enantiomeric excess values were determined by HPLC on a Chiralcel OD-H as chiral column. NMR spectra were recorded in a Bruker DRX-500 and Bruker DPX-300 spectrometers. ^1H NMR experiments were recorded in CDCl_3 at 500 MHz or 300 MHz at 20°C with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded in CDCl_3 at 125 MHz or 75 MHz and at 20°C . Optical rotations were obtained on Perkin Elmer 343, values were determined using the sodium lamp and the concentration was reported on $g/100 \text{ mL}$. Microanalysis for all new compounds was performed in the analytical laboratory of the Alcalá de Henares University.

Ethyl (*S*)-*N*-(*trans*-2-butenoyl)-4,4-dimethyl pyrroglutamate (2). Over a THF solution (5 mL) of **1** (430 mg, 2.32 mmol) cooled to -78°C under argon atmosphere was added a solution of *n*-Buli 1.6M in hexanes (1.44 mL, 2.55 mmol) keeping on the temperature below -74°C . The mixture was stirred for 5 minutes at -78°C and a solution of *trans*-crotonylchloride (90% tech.

Grade) (0.4 mL, 4.17 mmol) in THF (2.5 mL) was added in 0.5 h, keeping on the temperature below $-74\text{ }^{\circ}\text{C}$. The reaction mixture was quenched with NH_4Cl (5 mL) at $-78\text{ }^{\circ}\text{C}$ and allowed to warm to room temperature. The organic phase was separated and the aqueous phase washed with Et_2O (2x5 mL). The combined organic layers were dried over MgSO_4 , filtered and the solvent evaporated under reduced pressure. The residue was purified by chromatography NP-HPLC [Kromasil 60 (10 μm , 8x18 cm)] using hexane/acetone 85:15 to give 450 mg (76%) of **2**. A second purification by chiral NP-HPLC [Chiralcel OD (10 μm , 2x25 cm) 12 ml/min] gives 311 mg (ee > 98%).

$[\alpha]_{\text{D}}^{21} = -32.6^{\circ}$ (c 0.40, CH_2Cl_2); Lit.^{16,17} $[\alpha]_{\text{D}}^{21} = -34.5^{\circ}$ (c 0.31, CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.28 (d, 1H, $J = 15.4$ Hz, H7); 7.06-7.28 (m, 1H, H8); 4.65 (dd, 1H, $J = 5.0, 9.2$ Hz, H2); 4.21 (q, 2H, $J = 7.2$ Hz, OCH_2CH_3); 2.23 (dd, 1H, $J = 9.6, 13.4$ Hz, H3a); 1.87-1.97 (m, 4H, Me-9, H3b); 1.27 (t, 3H, $J = 7.2$ Hz, OCH_2CH_3); 1.24 (s, 3H, Me-10); 1.22 (s, 3H, Me-11). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 183.1, 174.6, 170.9, 145.9, 122.2, 60.6, 54.2, 51.8, 43.5, 34.9, 24.7, 23.7, 13.0.

Cyclopropanation Reactions

Ethyl (S)-4,4-dimethyl-N-(2-ethoxycarbonyl-3-methylcyclopropanecarbonyl)pyroglutamate (**3**)

Method A. A solution of (EDSA)¹⁹ (124 mg, 0.54 mmol) and DBU (82 μL , 0.54 mmol) in toluene was stirred at room temperature for 30 minutes under argon. Then, was added **2** (90 mg, 0.36 mmol) in toluene (1 mL) and the mixture was stirred at room temperature for 90 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL), extracted with Et_2O (3x10 mL) and the organic phase dried over MgSO_4 . The solvent was evaporated in vacuo and the residue purified by chromatography on silica gel with hexane/EtOAc 9:1 to give a mixture of **3a-d** (63%).

Method B. A solution of (EDSA) (500 mg, 2.2 mmol) and DBU (0.34 mL, 2.2 mmol) in THF/ CH_3CN (2:1) was stirred at room temperature for 30 minutes under argon. Then, was **2** added (380 mg, 1.5 mmol) in toluene (1 mL) and the mixture was stirred at room temperature for 36 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL), extracted with Et_2O (3x10 mL) and the organic phase dried over MgSO_4 . The solvent was evaporated under reduced pressure and the residue purified by chromatography with hexane/EtOAc (9:1) to give a mixture of **3a-d** (87%). Cyclopropanes **3a-d** were separated by semiprep-HPLC.

Ethyl (2S)-1-[(1S,2S,3S)-2-ethoxycarbonyl-3-methyl-cyclopropanecarbonyl]-4,4-dimethyl-5-oxo-pyrrolidine-2-carboxylate (3a**).** ^1H NMR (500 MHz, CDCl_3) δ (ppm) 1.25 - 1.30 (m, 12 H, Me-10, Me-11, 2 CH_2CH_3) 1.34 (d, $J = 6.4$ Hz, 3 H, Me-12) 1.88 - 1.97 (m, 2 H, H9 and H3a) 2.24 (dd, $J = 13.3, 9.6$ Hz, 1 H, H3b) 2.42 (dd, $J = 9.6, 4.7$ Hz, 1 H, H8) 3.67 (t, $J = 5.2$ Hz, 1 H, H7) 4.14 - 4.25 (m, 4 H, 2 CH_2CH_3) 4.59 (dd, $J = 9.5, 4.9$ Hz, 1 H, H2). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 179.5, 171.1, 170.0, 169.3, 61.3, 60.7, 55.1, 42.5, 35.9, 29.1, 29.0, 25.7, 25.6, 25.1, 14.0, 11.3. Anal. calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_6$: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.22; H, 7.17; N, 3.96.

Ethyl (2S)-1-[(1S,2S,3R)-2-ethoxycarbonyl-3-methyl-cyclopropanecarbonyl]-4,4-dimethyl-5-oxo-pyrrolidine-2-carboxylate (3b). ¹H NMR (500 MHz, CDCl₃) δ (ppm) 1.19 (d, *J* = 6.4 Hz, 3 H, Me-12) 1.25 - 1.30 (m, 12 H, Me-10, Me-11, 2 CH₂CH₃) 1.96 (dd, *J* = 13.4, 4.6 Hz, 1 H, H3a) 2.04 - 2.12 (m, 1 H, H9) 2.25 (dd, *J* = 13.4, 9.8 Hz, 1 H, H3b) 2.31 (t, *J* = 5.2 Hz, 1 H, H8) 3.69 (dd, *J* = 10.1, 4.9 Hz, 1 H, H7) 4.11 - 4.24 (m, 4 H, 2 CH₂CH₃) 4.63 (dd, *J* = 9.6, 4.7 Hz, 1 H, H2). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 179.4, 171.2, 170.0, 169.5, 61.2, 60.7, 55.2, 42.6, 35.8, 29.0, 27.8, 25.8, 25.3, 25.1, 14.0, 10.9. Anal. calcd for C₁₇H₂₅NO₆: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.21; H, 7.17; N, 3.97.

Ethyl (2S)-1-[(1R,2R,3R)-2-ethoxycarbonyl-3-methyl-cyclopropanecarbonyl]-4,4-dimethyl-5-oxo-pyrrolidine-2-carboxylate (3c). ¹H NMR (500 MHz, CDCl₃) δ (ppm) 1.24 - 1.35 (m, 15 H, Me-10, Me-11, Me-12, 2 CH₂CH₃) 1.83-1.91 (m, 1 H, H9) 1.95 (dd, *J* = 13.3, 5.3 Hz, 1 H, H3a) 2.24 (dd, *J* = 13.1, 9.5 Hz, 1 H, H3b) 2.45 (dd, *J* = 9.5, 4.6 Hz, 1 H, H8) 3.66 (t, *J* = 5.2 Hz, 1 H, H7) 4.15 - 4.25 (m, 4 H, 2 CH₂CH₃) 4.60 (dd, *J* = 9.5, 5.2 Hz, 1 H, H2). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 179.2, 170.9, 170.8, 169.6, 61.3, 60.6, 55.1, 42.4, 35.9, 29.1, 29.0, 25.6, 25.5, 25.0, 13.9, 11.2. Anal. calcd for C₁₇H₂₅NO₆: C, 60.16; H, 7.42; N, 4.13. Found: C, 60.22; H, 7.17; N, 3.96.

Ethyl (2S)-4,4-dimethyl-N-(2-methyl-4-oxo-5-oxaspiro[2.4]heptan-1-carbonyl) pyroglutamate (4). To a solution of the Trost's salt²⁰ (695 mg, 2.97 mmol) in THF/CH₃CN (2:1), NaH (72 mg, 2.97 mmol) was slowly added at room temperature under argon. When evolution of hydrogen was finished, **2** (500 mg, 1.98 mmol) in THF (5 mL) was added and the mixture was heated at reflux temperature for 12 h. Then the reaction mixture was quenched with a saturated solution of NH₄Cl (10 mL), extracted with CH₂Cl₂ (3×15 mL) and the organic phase dried over MgSO₄. The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel. Elution with hexane/EtOAc (7:3) allowed to separate compounds **4a** and **4b** (80% yield, 4:1 ratio) and a mixture of **4c/4d** (11% yield, 4:1 ratio by ¹H NMR).

Ethyl (2S)-N-[(1S,2S,3R)-(2-methyl-4-oxo-5-oxaspiro[2.4]heptan-1-carbonyl)]-4,4-dimethylpyroglutamate (4a). White solid. Mp: 86-87°C. [α]_D²¹ = -35.8° (c 1.25, CDCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 1.21 - 1.29 (m, 9 H, Me-10, Me-11, CH₂CH₃) 1.35 (d, *J* = 6.3 Hz, 3 H, Me-12) 1.93 (dd, *J* = 13.2, 4.7 Hz, 1 H, H3a) 2.02 - 2.09 (m, 1 H, H9) 2.21 - 2.26 (m, 2 H, H3b, H13a) 2.35 - 2.42 (m, 1 H, H13b) 3.62 (d, *J* = 6.6 Hz, 1 H, H7) 4.19 (q, *J* = 7.1 Hz, 2 H, CH₂CH₃) 4.31 - 4.39 (m, 2 H, CH₂-14) 4.61 (dd, *J* = 9.6, 4.6 Hz, 1 H, H2). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 179.3, 175.2, 170.5, 66.2, 61.6, 55.0, 35.9, 34.8, 34.2, 28.7, 27.8, 26.1, 25.8, 25.1, 14.0, 11.0. IR (KBr) 3460, 2983, 2360, 1772, 1747, 1682, 1456, 1374, 1286, 1200, 1019 cm⁻¹. MS (Electrospray): 360.0 (M⁺ + Na⁺), 338.1 (M⁺ + 1). Anal. calcd for C₁₇H₂₃NO₆: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.24; H, 6.92; N, 3.85.

Ethyl (2S)-N-[(1R,2R,3R)-(2-methyl-4-oxo-5-oxaspiro[2.4]heptan-1-carbonyl)]-4,4-dimethylpyroglutamate (4b). Colourless oil. [α]_D²¹ = -0.8° (c 0.91, CDCl₃). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 1.20 - 1.27 (m, 12 H, Me-10, Me-11, Me-12, CH₂CH₃) 1.98 (dd, *J* = 13.4, 3.6 Hz, 1 H, H3a) 2.23 (dd, *J* = 13.2, 10.1 Hz, 1 H, H3b) 2.30 - 2.39 (m, 2 H, H9, H13a, H9) 2.44 - 2.51 (m, 1 H, H13b) 2.54 (d, *J* = 7.6 Hz, 1 H, H7) 4.12 - 4.28 (m, 2 H, CH₂CH₃) 4.41 - 4.50 (m, 2 H, CH₂-14) 4.59 (dd, *J* =

9.8, 3.8 Hz, 1 H, H2). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 180.4, 174.8, 170.5, 166.5, 65.9, 61.7, 55.2, 42.3, 39.9, 36.1, 32.8, 27.1, 26.1, 25.1, 22.0, 13.7, 13.2. IR (NaCl) 3531, 2974, 2935, 1768, 1739, 1698, 1455, 1375, 1335, 1275, 1210, 1131 cm^{-1} . MS (Electrospray): ($\text{M}^+ + \text{Na}^+$) 360.1, ($\text{M}^+ + 1$) 338.1. Anal. calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 59.95; H, 6.97; N, 4.25.

Reaction of (4a) with nucleophiles

Reaction with alkoxides. General procedure

To a solution of **4a** (50 mg, 0.15 mmol) in the corresponding alcohol (2 mL), the alkoxide (0.15 mmol) was added and the mixture was stirred at room temperature for 30 minutes. Then the solvent was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2 (10 mL). The solution was washed with a saturated solution of NaCl (3 \times 5 mL), the organic phase dried with MgSO_4 , the solvent evaporated under reduced pressure and the residue purified by column chromatography using hexane/EtOAc (7:3) as eluent.

(1S, 2S, 3R)-2-Ethyl-1-methoxycarbonyl-4-oxo-5-oxaspiro[2,4]heptane (5a). Colourless oil. 80% yield. $[\alpha]_{\text{D}}^{21} = +71.0^\circ$ (c 1.00, CDCl_3). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 4.41 (ddd, 1H, $J = 3.3, 9.0, 19.8$ Hz, H7a); 4.34 (m, 1H, H7b); 4.14 (q, 2H, $J = 7.1$ Hz, OCH_2CH_3); 2.46 (m, 1H, H6a); 2.30 (ddd, 1H, $J = 3.3, 7.3, 13.4$ Hz, H6b); 2.19 (d, 1H, $J = 6.4$ Hz, H2); 1.88 (q, 1H, $J = 6.4$ Hz, H4); 1.29 (d, 3H, $J = 6.4$ Hz, CH_3); 1.26 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 175.3, 170.5, 66.5, 61.1, 33.0, 32.7, 29.8, 28.6, 14.2, 11.2. IR (NaCl) 3369, 2983, 2933, 2360, 1766, 1726, 1455, 1374, 1314, 1239, 1188, 1138, 1110, 1028 cm^{-1} . MS (Electrospray): ($\text{M}^+ + \text{Na}^+$) 221.1; ($\text{M}^+ + 1$) 199.1. Anal. calcd for $\text{C}_{10}\text{H}_{14}\text{O}_4$: C, 60.59; H, 7.12. Found: C, 60.37; H, 6.94

(1S, 2S, 3R)-2-Methyl-1-methoxycarbonyl-4-oxo-5-oxaspiro[2,4]heptane (5b). Colourless oil. 85% yield. $[\alpha]_{\text{D}}^{21} = +64.0^\circ$ (c 0.91, CDCl_3). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 4.41 (ddd, 1H, $J = 18.3, 9.2, 3.3$ Hz, H7a); 4.36 (ddd, 1H, $J = 18.3, 9.0, 1.5$ Hz, H7b); 3.70 (s, 3H, OCH_3), 2.46 (ddd, 1H, $J = 18.7, 9.2, 9.0$ Hz, H6a); 2.31 (ddd, 1H, $J = 13.4, 3.3, 1.5$ Hz, H6b); 2.20 (d, 1H, $J = 6.4$ Hz, H2); 1.88 (q, 1H, $J = 6.4$ Hz, H4); 1.29 (d, 3H, $J = 6.4$ Hz, CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 175.5, 168.2, 65.6, 52.3, 36.7, 31.2, 26.7, 23.3, 13.2. IR (NaCl) 2962, 2935, 1766, 1732, 1445, 1375, 1339, 1240, 1198, 1028 cm^{-1} . MS (Electrospray): 207.0 ($\text{M}^+ + \text{Na}^+$), 185.1 ($\text{M}^+ + 1$). Anal. calcd for $\text{C}_9\text{H}_{12}\text{O}_4$: C, 58.69; H, 6.57. Found: C, 58.57; H, 6.46.

(1S,2S,3S)-2-Methyl-1-(morpholino-4-carbonyl)-5-oxaspiro[2,4]-4-heptanone (5c). A mixture of **4a** (0.15 mmol) and morpholine (0.15 mmol) in THF (3 mL) was stirred at reflux temperature for 24 h under argon. Then the reaction mixture was treated with a saturated solution of 1N de HCl (5 mL) and extracted with CH_2Cl_2 (3 \times 10 mL). The organic phase was washed with a saturated solution of NaCl (2 \times 10 mL) and dried over MgSO_4 . The solvent was eliminated under reduced pressure and the residue purified by column chromatography using hexane/EtOAc 6:4 as eluent. Colourless oil. 70% yield. $[\alpha]_{\text{D}}^{21} = +29.0^\circ$ (c 1.15, CDCl_3). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 4.30-4.50 (m, 2H, H7); 3.51 (m, 8H, $\text{NCH}_2\text{CH}_2\text{O}$); 2.16-2.46 (m, 2H, H6); 2.30 (d, 1H, $J = 7.0$

Hz, H2); 2.08 (q, 1H, $J = 7.0$ Hz, H4); 1.30 (d, 3H, $J = 7.0$ Hz, CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 176.1, 163.3, 66.9, 66.8, 66.7, 46.0, 42.4, 32.3, 31.5, 28.7, 28.5, 11.3. IR (NaCl) 3431, 2959, 2922, 2856, 1756, 1649, 1450, 1380, 1233, 1107, 1011 cm^{-1} . MS (Electrospray): 262.1 ($\text{M}^+ + \text{Na}^+$), 240.1 ($\text{M}^+ + 1$). Anal. calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.19; H, 7.24; N, 5.76.

(1S,2S,3S)-1-Benzoyl-2-methyl-5-oxaspiro[2,4]-4-heptanone (5d). To a solution of **4a** (0.15 mmol) in THF (3 mL), phenylmagnesium bromide (0.15 mmol) was added at -40°C under argon and the mixture was stirred at room temperature for 4 hours. Then the reaction mixture was treated with a saturated solution of NH_4Cl (10 mL), allowed to warm to room temperature and extracted with CH_2Cl_2 (3×10 mL). The organic phase was dried with MgSO_4 , the solvent evaporated under reduced pressure and the residue chromatographed using hexane/EtOAc (8:2). Colourless oil. 73% yield. $[\alpha]_D^{21} = +86.5^\circ$ (c 0.81, CDCl_3). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.97-8.01 (m, 2H, H arom); 7.42-7.66 (m, 3H, H arom); 4.41 (t, 2H, $J = 7.9$ Hz, H7); 3.25 (m, 1H, H2); 2.37 (m, 2H, H6); 2.22(q, 1H, $J = 6.4$ Hz, H4); 1.41 (d, 3H, $J = 6.4$ Hz, CH_3). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 196.1, 175.7, 137.4, 133.5, 128.7, 128.2, 66.6, 36.6, 36.1, 30.7, 28.1, 11.4. IR (NaCl) 2962, 2928, 2873, 1762, 1641, 1597, 1575, 1449.2, 1374, 1239, 1135 cm^{-1} . MS (Electrospray): 253.1 ($\text{M}^+ + \text{Na}^+$), 231.1 ($\text{M}^+ + 1$). Anal. calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3$: C, 73.03; H, 6.13. Found: C, 73.12; H, 6.09.

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