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Captodative α,β-unsaturated oxazolines as dienophiles in the asymmetric Diels-Alder reaction

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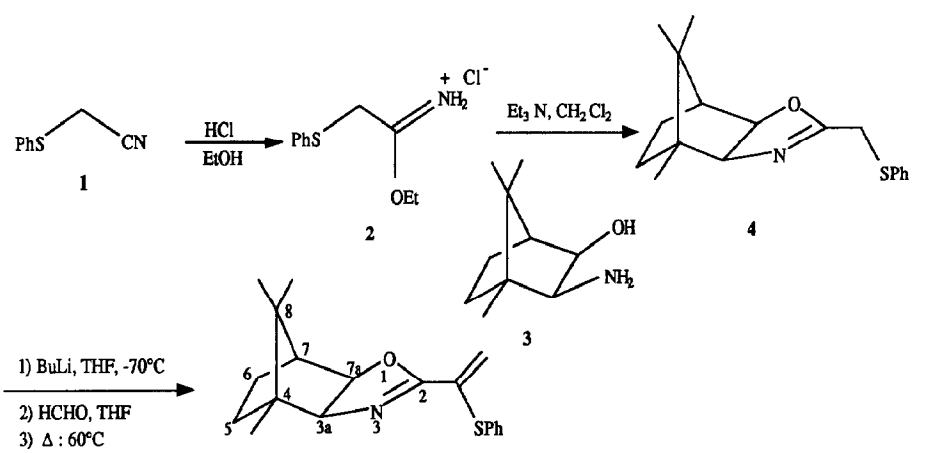
Summary : Captodative oxazoline derivative **5a** gave rise to four-cycloadducts **6**, **7**, **8** and **9** in the presence of trifluoroacetic anhydride and cyclopentadiene. Hydrolysis of **6** led to α-phenylthio carboxylic acid **14**.

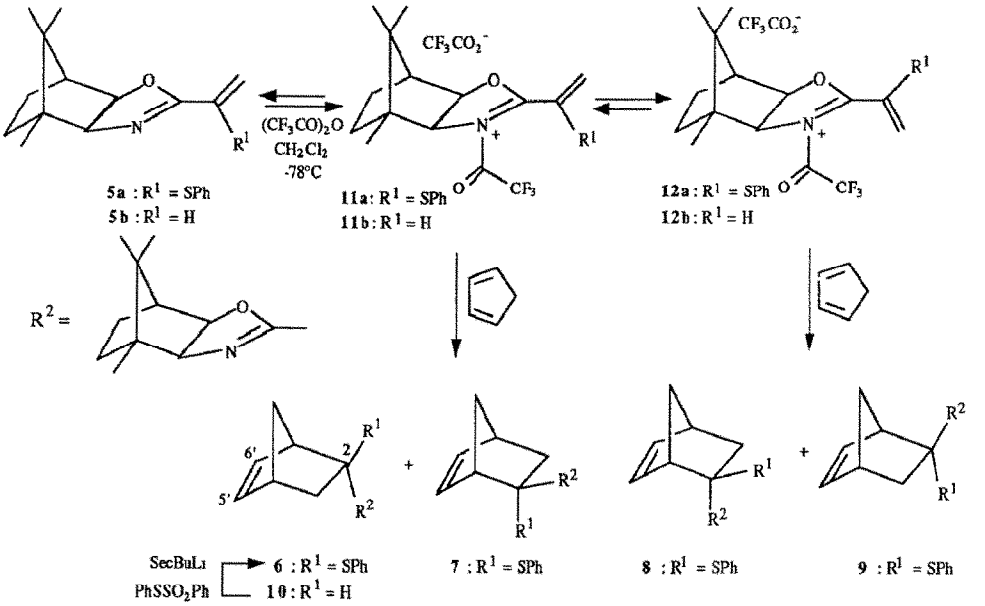
Chiral α,β-unsaturated oxazolines proved to be powerful dienophiles in the Diels Alder cycloaddition (1). In order to extend the scope of application of this reaction, we now wish to report about the use of captodative α,β-unsaturated oxazolines (2) in the asymmetric Diels-Alder cyclisation. Indead it has been demonstrated that captodative olefines showed increasing reactivity in [4+2] cycloadditions (3,4). Otherwise, the stereoselectivity of such cycloaddition could give further, information concerning the previously postulated transition state (1). Lastly, captodative olefines can be considered as ketene equivalents and are useful synthetic intermediates (5).

Thus, phenylthio acetonitrile **1** after treatment with hydrochloric acid in anhydrous ethanol afforded quantitatively the corresponding iminoether hydrochloride **2**. Condensation of this salt with aminoalcohol **3** (1) in the presence of triethylamine (6) gave rise to the oxazoline derivative **4** (7). After deprotonation with BuLi, the azaenolate intermediate was treated with a solution of formaldehyde in tetrahydrofuran (8). The unstable oxazoline alcohol intermediate was dehydrated without isolation and afforded the anticipated unsaturated oxazoline **5a** (9) (Scheme I).



Scheme I

Oxazoline **5a** subjected to the usual cycloaddition conditions (1) in the presence of trifluoroacetic anhydride and cyclopentadiene at -78°C afforded four adducts **6**, **7**, **8** and **9** (ratio 65:8:23:4). Configurations of these compounds were determined by chemical correlation and by examination of their ^1H NMR spectra. Thus cycloadduct **6** has been independently prepared by thiophenylation of adduct **10** of known absolute configuration (1). The configuration at C-2 in compounds **7**, **8** and **9** was deduced from the chemical shifts of the olefinc protons at C-5' and C-6' (Scheme II).



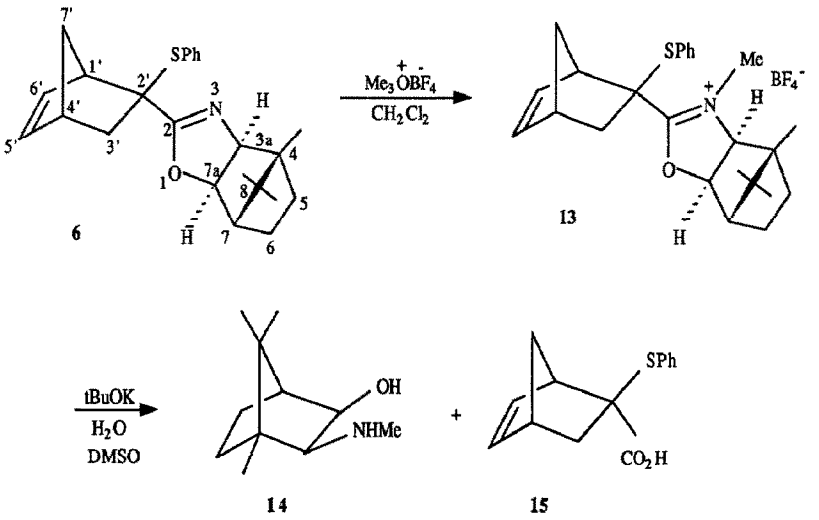
Scheme II

It appeared that oxazoline **5a** after acylation with trifluoroacetic anhydride was at least as reactive as the acrylic oxazoline **5b**. But in contrast with the case of oxazoline **5b** giving rise to the major s-trans conformer **11b** and to nearly a single adduct **10** (1), the presence of a thiophenyl moiety on the acrylic side chain in oxazoline **5a** induced a modification in the equilibrium between the two oxazolinium salts conformers **11a** and **12a** (Scheme II). Thus, if we reasonably excluded any attack on the β-face of the camphor oxazoline derivatives owing to the presence of the methyl at C-8, adducts **6** and **7** should respectively result from the endo and the exo attack of cyclopentadiene on the s-trans conformer **11a** whereas adducts **8** and **9** should result from the endo and exo attacks on the s-cis conformer **12a**. However it is not possible to deduce the ratio of conformers **11a** : **12a** in equilibrium from the ratio of adducts **6**, **7**, **8** and **9** because the rate of cycloadditions could be quite different in each case. Finally, it is worthy of note that the fourth possible diastereomer **9** resulting from the exo attack on the s-cis conformer **12a** was detected in very small amounts in the reaction mixture. On the other hand, the total yield of cycloadditions (56%) was decreased by a competition between the [4+2] process and the [2+2] cycloaddition which often occured with captodative olefine giving rise to a cyclobutane derivative.

When a competitive experiment was carried out with equimolecular amount of cyclopentadiene, oxazoline **5a** and oxazoline **5b** in the presence of trifluoroacetic anhydride at -78°C, cycloadducts **6**, **7**, **8** and **9** were obtained in 68% yield in the ratio of 54 : 12 : 27 : 7 and cycloadduct **10** was isolated in 28% yield.

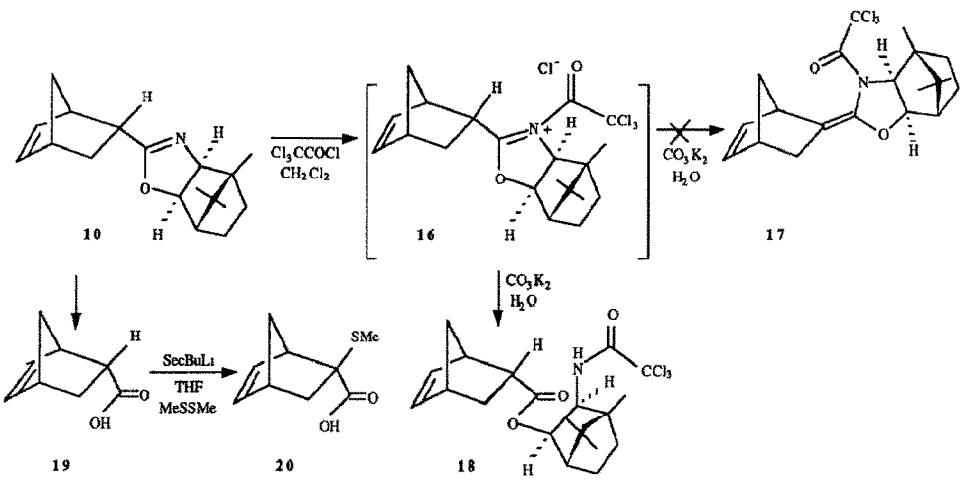
This result is in sharp contrast with the result obtained by Stella and al. (10) in a competitive experiment between acrylonitrile and 2-methylthio acrylonitrile with cyclohexadiene. In this reaction, the captodative olefine proved to be substantially more reactive than the classical dienophile. We believe that, in our case, the captodative effect could be over come by the great reactivity of the trifluoroacyl oxazolinium moiety. Perhaps a study of cycloadditions with less reactive dienes than cyclopentadiene should be more informative about this point.

Hydrolysis of the oxazoline ring in adduct **6** proved to be rather difficult. The previously developed method (1) ($ClCO_2Bn$, Na_2CO_3, CH_2Cl_2, H_2O ; NaOH, H_2O, MeOH) was ineffective in that case. However, N-alkylation of **6** with trimethyl oxonium tetrafluoroborate led to the expected oxazolinium salt **13** (11). Hydrolysis of this salt under modified Gassman conditions (12) (ter-BuOK, H_2O, DMSO) allowed the recovery of N-methylaminoalcohol **14** (71%) and of carboxylic acid **15** (60% after purification) (Scheme III). Nevertheless, this sequence of reactions didn't allowed the recovery of the chiral auxiliary itself, aminoalcohol **3**.



Scheme III

In order to develop the use of α,β-unsaturated oxazolines as new chiral ketene equivalent, two approaches were successively studied with the readily prepared adduct **10** as starting material. The straight forward method developed by Barton for the degradation of the side chain of cholic acid (13) was first examined. Thus adduct **10** was treated with trichloroacetyl chloride but the deprotonation of the acyl oxazolinium intermediate **16**, a rather unstable species, was unsuccessfull. In fact, this compound by a nucleophilic attack of hydroxyle anion afforded readily the amide ester **18** (Scheme IV). This difference of behaviour with the Barton's example is probably due to the fact that the oxazoline ring is fused with a [2.2.1] bicyclic framework. Opening of oxazolinium moiety, the only observed reaction, bring a decompression of the molecule.



Scheme IV

Thus we turned to the Trost oxidative decarboxylation (14). After hydrolysis of the oxazoline ring in adduct **10** as described previously (1), carboxylic acid **19** was deprotonated and treated with sec.BuLi and dimethyldisulfide in tetrahydrofuran affording compound **20** (Scheme IV). Transformation of α-methylthio carboxylic acid **20** into the corresponding ketone has been already described (15). In this sequence of reactions, α,β-unsaturated oxazoline can be regarded as formal chiral ketene equivalent. However more direct transformation are under investigation.

Experimental Section

IR spectra (ν (cm^{-1}), CH_2Cl_2 were recorded on a Nicolet 205 FT.IR spectrophotometer and $[\alpha]_D$ were measured on a Perkin-Elmer 241 in chloroform and the concentrations were given in g/100 mL. ^1H NMR spectra were obtained on Brucker WM 200 and AC 200 spectrometers (δ = 0 (TMS), $CDCl_3$. Coupling constants, *J*, were given in hertz; s, d, t, dd and m, respectively indicated singlet, doublet, triplet, doublet of doublets, and multiplet. Mass spectra were measured on a AEI MS 50 spectrometer. GC-MS spectra and chromatograms were recorded on a INCOS 50 mass spectrometer coupled with a Varian 3400 chromatograph (capillary column DB5 (25 M)) and a Finnigan Mat computer. HPLC separations were performed on a Waters chromatograph coupled with a PDA Detector 990. Preparative thin-layer chromatographies (preparative TLC) were performed with Kieselgel HF 254 (Merck) and flash column chromatography on Kielselgel 60 (230-400 mesh, Merck).

Extraction means that the reaction medium was extracted with dichloromethane, washed successively with water and with brine, dried over magnesium sulfate, filtrated, and evaporated under vacuum.

Tetrahydrofuran (THF), toluene, and ether were distilled from sodium metal-benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Trifluoroacetic anhydride was distilled under argon from phosphorus pentoxide just before use.

Preparation of oxazoline 4

To a solution of amino alcohol **3** (717 mg, 4.24 mmol) and imino ether hydrochloride **2** (980 mg, 4.24 mmol) in dichloromethane (20 mL) was added, under argon at room temperature, a solution of triethylamine

(2.4 mL, 4 eq., 17 mmol) in dichloromethane (3 mL). The reaction medium was stirred for 4 h at room temperature. After extraction with dichloromethane and column chromatography (SiO_2, CH_3CO_2Et 30 heptane 70) oxazoline **4** was isolated (915 mg, 72%).

NMR ^1H : 7.37 (m, 5H aromatics) ; 4.52 (d, 1H, J = 8.6 Hz, C_{7a}-H) ; 3.86 (d, 1H, J = 8.6 Hz, C_{3a}-H) ; 3.75 (d, 1H, J = 15 Hz, CH-SPh) ; 3.56 (d, 1H, J = 15 Hz, CH-SPh) ; 2.15 (d, 1H, C_7-H) ; 1.08 (s, 3H) ; 0.94 (s, 3H) ; 0.87 (s, 3H). IR : 2956, 1656, 1482, 997. MS *m/z* : 301 (M^+) 268 (100), 191, 123, 95, 82.$[\alpha]_D$ = -86 (c = 1.44).

Preparation of captodative oxazoline 5a

To a solution of oxazoline **4** (148 mg, 0.49 mmol) in anhydrous THF (3 mL) was added under argon at -78°C a solution of BuLi (1.6M) in hexane (1.2 eq., 0.37 mL, 0.98 mmol). The yellow reaction medium was stirred 1 h at -78°C. Then a large excess of formaldehyde solution in THF (8) was added. The reaction medium faded rapidly. After stirring for 1 h at -78°C, the resulting solution was warmed to room temperature and finally stirred for 15 h. After extraction and purification (SiO_2, CH_3CO_2Et 20 heptane 80) oxazoline **5a** was isolated (79 mg, 51%).

NMR ^1H : 7.58 (m, 2H aromatics) ; 7.42 (m, 3H aromatics) ; 6.0 (s, 1H) ; 5.05 (s, 1H) ; 4.53(d, 1H, J = 8.2 Hz, C_{7a}-H) ; 4.0 (d, 1H, J = 8.2 Hz, C_{3a}-H) ; 2.0 (d, 1H, C_7-H) ; 1.10 (s, 3H) ; 0.90 (s, 3H) ; 0.86 (s, 3H). IR : 2956, 1644, 1583, 1082, 997. MS *m/z* : 313 (M^+) 202 (100), 135, 95.$[\alpha]_D$ = -71 (c = 1.27).

Preparation of cycloadduits 6, 7, 8 and 9

To a solution of oxazoline **5a** (116 mg, 0.37 mmol) in anhydrous dichloromethane (4 mL) was added under argon, at -20°C trifluoroacetic anhydride (3 eq., 0.16 mL, 1.11 mmol). The reaction medium was stirred for 5 mn at -20°C. Then cyclopentadiene (6.5 eq., 0.2 mL, 2.4 mmol) was added at -78°C. The reaction medium was stirred for 1 h at -78°C. After extraction and first purification (SiO_2, CH_3CO_2Et 20 heptane 80) a mixture of four products (78 mg, 56%) was isolated. The ratio **7**, **8**, **9** and **6** was determined by HPLC : 8, 23, 4, 65. A second purification (SiO_2, heptane 80, ether 20) allowed to isolate a mixture of three products **7**, **8** or **9** (25 mg, 18%) which was further purified and a pure product **6** (53 mg, 38%).

In order of decreasing polarity.

7 : NMR ^1H : 7.49 (m, 2H aromatics) ; 7.32 (m, 3H aromatics) ; 6.34 (br s, 2H, $C_{5',6'}$-H) ; 4.36 (d, 1H, J = 9 Hz, C_{7a}-H) ; 3.50 (d, 1H, J = 9 Hz, C_{3a}-H) ; 2.90 (br s, 1H) ; 0.97 (s, 3H) ; 0.90 (s, 3H) ; 0.87 (s, 3H). IR : 2996, 1640, 1018, 998. MS *m/z* : 379 (M^+), 314, 203, 202, 160, 135, 134, 95, 91 (100). $[\alpha]_D$ = -55 (c = 0.27).

8 : NMR ^1H : 7.47 (m, 2H aromatics) ; 7.28 (m, 3H aromatics) ; 6.36 and 6.27 (2m, 2H, $C_{6'}$-H and $C_{5'}$-H) ; 4.13 (d, 1H, J = 9 Hz, C_{7a}-H) ; 3.55 (d, 1H, J = 9 Hz, C_{3a}-H) ; 3.40 (br s, 1H) ; 2.98 (br s, 1H) ; 2.12 (d, J = 5 Hz, C_7-H) ; 1.0 (s, 3H) ; 0.90 (s, 3H) ; 0.80 (s, 3H). IR : 2955, 1637, 1005. MS *m/z* : 379 (M^+, 100), 314, 203, 202, 160, 135, 134, 95, 91. $[\alpha]_D$ = -120 (c = 0.91).

9 : NMR ^1H : 7.47 (m, 2H aromatics) ; 7.33 (m, 3H aromatics) ; 6.1 and 6.06 (2m, 2H, $C_{5'}$-H and $C_{6'}$-H) ; 4.43 (d, 1H, J = 9 Hz, C_{7a}-H) ; 3.54 (d, 1H, J = 9 Hz, C_{3a}-H) ; 3.13 (br s, 1H) ; 2.87 (br s, 1H) ; 0.98 (s, 3H) ; 0.83 (s, 3H) ; 0.77 (s, 3H). IR : 2959, 1647. MS *m/z* : 379 (M^+, 100), 351, 313, 312, 270, 203, 202, 160, 95, 91. .

6 : RMN ^1H : 7.57 (m, 2H aromatics) ; 7.33 (m, 3H aromatics) ; 6.14 and 5.94 (2m, 2H, $C_{6'}$-H and $C_{5'}$-H) ; 3.97 (d, 1H, J = 9.2 Hz, C_{7a}-H) ; 3.75 (d, 1H, J = 9.2 Hz, C_{3a}-H) ; 3.10 (br s, 1H) ; 2.89 (br s, 1H) ; 0.98 (s,

3H) ; 0.74 (s, 6H). IR : 2956, 1641, 1020. MS *m/z* : 379 (M^+), 313, 270 (100), 203, 202, 160, 91. $[\alpha]_D$ = +54 (c = 1.73).

Competitive experiment between oxazolines 5a and 5b

To a solution of captodative oxazoline **5a** (31.5 mg, 0.10 mmol) and oxazoline **5b** (20.6 mg, 0.10 mmol) in dichloromethane (2 mL) was added successively, under argon, at -78°C, trifluoroacetic anhydride (0.24 mmol, 0.034 mL) and cyclopentadiene (0.10 mmol, 0.008 mL). The reaction medium was stirred 1 h at -78°C. After extraction and purification (SiO_2, CH_3CO_2Et 20 heptane 80) cycloadducts **7**, **8**, **9** and **6** from oxazoline **5a** (26 mg, 68%) in ration 11, 27, 7 and 54 and cycloadduct **10** from oxazoline **5b** (7 mg, 26%) were isolated.

Chemical correlation with cycloadduct 10

To a solution of cycloadduct **10** (24 mg, 0.09 mmol) in anhydrous THF (1 mL) was added under argon, at -78°C a solution of sec BuLi (1.3M) in cyclohexane/hexane (1.3 eq., 0.09 mL, 0.12 mmol). The yellow reaction medium was stirred for 30 min at -78°C. Then a solution of $PhSSO_2Ph$ (1.3 eq., 29 mg, 0.12 mmol) in anhydrous THF (1 mL) was added. The reaction medium faded and was stirred for additional 20 min at -70°C. After extraction and purification (SiO_2, heptane 90 CH_3CO_2Et 10) cycloadduct **6** was isolated (26 mg, 77%).

6 : NMR ^1H : 7.56 (m, 2H aromatics) ; 7.33 (m, 3H aromatics) ; 6.11 and 5.93 (2m, 2H, $C_{5'}$-H and $C_{6'}$-H) ; 3.95 (d, 1H, J = 9.2 Hz, C_{7a}-H) ; 3.71 (d, 1H, J = 9.2 Hz, C_{3a}-H) ; 3.10 (br s, 1H) ; 2.89 (br s, 1H) ; 0.99 (s, 3H) ; 0.77 (s, 6H). IR : 2956, 1640, 1020. MS *m/z* : 379 (M^+), 313, 270 (100), 203, 202, 160, 91. $[\alpha]_D$ = +60 (c = 1.40).

Preparation of oxazolinium salt 13

To a solution of trimethyloxonium tetrafluoroborate (9 mg, 0.06 mmol) in dichloromethane (0.5 mL) was added, under argon, at 0°C, a solution of cycloadduct **6** (21 mg, 0.06 mmol) in dichloromethane (1 mL). The reaction medium was stirred for 20 hours at room temperature and evaporated under vacuum. Oxazolinium **13** was quantitatively isolated.

NMR ^1H : 7.54 (m, 5H aromatics) ; 6.29 and 5.87 (2m, 2H, $C_{5'}$-H and $C_{6'}$-H) ; 4.70 (d, 1H, J = 9 Hz, C_{7a}-H); 4.47 (d, 1H, J = 9 Hz, C_{3a}-H) ; 3.79 (s, 3H, N-CH_3) ; 3.21 (br s, 1H) ; 3.10 (br s, 1H) ; 1.20 (s, 3H) ; 0.87 (s, 3H) ; 0.70 (s, 3H). IR : 2963, 1622, 1002. $[\alpha]_D$ = +83 (c = 1.03).

Hydrolysis reaction. Preparation of aminoalcohol 14 and carboxylic acid 15

A solution of potassium ter-butoxide (8 eq., 73 mg, 0.65 mmol) and water (2 eq., 0.003 mL, 0.16 mmol) in DMSO (0.5 mL) was stirred 5 min at 0°C. A solution of oxazolinium **13** (39 mg, 0.081 mmol) in DMSO (0.5 mL) was added dropwise. After 2 hours at room temperature, the oxazolinium gave rise to a less polar amino ester intermediate. Then the reaction medium was stirred 4 h at 50°C. After extraction with ether, N-methylaminoalcohol **14** was almost quantitatively isolated (14 mg). The basic aqueous solution was acidified with an aqueous solution of hydrochloric acid (10N) and extracted with ether. After purification (SiO_2, CH_3CO_2Et 30 heptane 70) the carboxylic acid **15** was isolated (12 mg, 60%).

14 : NMR ^1H : 3.71 (d, 1H, J = 7.8 Hz, C_3-H) ; 2.86 (s, 2H, OH and NH) ; 2.55 (d, 1H, J = 7.8 Hz, C_2-H) ; 2.51 (s, 3H, N-CH_3) ; 1.01 (s, 3H) ; 0.92 (s, 3H) ; 0.77 (s, 3H). MS *m/z* : 183 (M^+), 154, 126, 112 (100), 95, 84, 73.

15 : NMR ^1H : 7.53 (m, 2H aromatics) ; 7.35 (m, 3H aromatics) ; 6.27 and 6.01 (2m, 2H, C_5-H and C_6-H) ; 3.0 (br s, 1H) ; 2.94 (br s, 1H). IR : 3500 - 2800 (broad band), 1697. MS *m/z* : 246 (M^+), 180 (100), 135, 91. $[\alpha]_D$ = +21 (c = 0.67).

Preparation of compound 20

To a solution of 5-norbornene 2-carboxylic acid **19** (59 mg, 0.43 mmol) in dry THF (1 mL) was added, under argon, at -78°C a solution of sec-BuLi (1.3M) in cyclohexane/hexane (2.5 eq., 0.82 mL, 1.08 mmol). The yellow solution was stirred 30 min at -70°C. Then dimethyl disulfide (1.5 eq., 0.06 mL, 0.64 mmol) was added. The reaction medium was stirred for additional 30 min at -78°C. The mixture after hydrolysis with an aqueous solution of hydrochloric acid (2N), was extracted with dichloromethane affording 71 mg of crude product. Crystallisation in pentane gave carboxylic acid **20** contaminated with small amount of isomer (50 mg, 63%). The ratio of the two isomers was calculated on the next compound : Methylester of **20** by gas chromatography - mass spectrometry.

NMR ^1H : 10.10 (br s, 1H, CO_2-H) ; 6.29 and 6.09 (2m, 2H, C_6-H and C_5-H) ; 3.11 (br s, 1H) ; 2.90 (br s, 1H) ; 2.22 (s, 3H, S-CH_3) three signals show the other isomer : 6.20 and 6.0 (2m) ; 3.42 (br s) ; 3.11 (br s). IR : 3500 - 2400 (broad band), 1694. MS *m/z* : 184 (M^+), 118, 91, 66 (100). $[\alpha]_D$ = +85 (c = 0.97).

MP (pentane) = 88-89°C.

Preparation of methylester of 20

Carboxylic acid **20** was treated with an excess of a freshly distillated solution of diazomethane in ether. The reaction medium was stirred for 10 min at room temperature and evaporated under vacuum. The ester was quantitatively isolated (10.8 mg). Analysis by gas chromatography - mass spectrometry showed two products at *m/e* 198 in a ratio 97.5 : 2.5.

NMR ^1H : major isomer : 6.26 and 6.01 (2m, 2H, C_6-H and C_5-H) ; 3.70 (s, 3H, CO_2CH_3) ; 3.14 (br s, 1H) ; 2.94 (br s, 1H) ; 2.18 (s, 3H, S-CH_3) ; minor isomer : 6.33 and 6.16 (2m) ; 3.80 (s). IR : 2970, 1740, 1621. MS *m/z* : 198 (M^+), 132 (100), 100, 91, 73, 66. $[\alpha]_D$ = +62 (c = 0.91).

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