Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 885–889

TETRAHEDRON: *ASYMMETRY*

Application of the asymmetric Diels–Alder reaction of a 2-substituted chiral maleate to the formal synthesis of (−)-β-santalene

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Received 16 April 2002; accepted 19 April 2002

Abstract—The asymmetric Diels–Alder addition of chiral 2-substituted maleates to cyclopentadiene is described and applied to the formal synthesis of (−)-β-santalene. © 2002 Published by Elsevier Science Ltd.

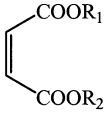
1. Introduction

Diels–Alder reactions of cyclopentadiene with dienophiles is a powerful method for the stereoselective construction of the bicyclo[2.2.1]heptane framework encountered in various terpenes and natural products. Asymmetric synthesis of the santalane sesquiterpenes have frequently been based on this reaction as a key step[1–4] because the appropriate choice of a chiral dienophile (often in combination with a Lewis acid) permits control of the stereochemistry of up to four stereogenic centers in a single operation.

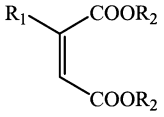
A large number of chiral dienophiles are available for asymmetric Diels–Alder reactions.[5] Acrylates or methacrylates of enantiomerically pure alcohols or amines are the most popular and fumarates were among the first reagents to be used in Diels–Alder addition catalyzed by organoaluminium Lewis acids: with Et_2AlCl, readily available dimenthyl fumarate adds to cyclopentadiene with a diastereoselectivity of 99%.[6]

The use of maleates as dienophiles in Diels–Alder reactions is much less common. Unsymmetrical maleates were introduced in asymmetric Diels–Alder reactions through a study[7] on the diastereoselectivity of the addition of maleates **1a–c** to cyclopentadiene (Fig. 1).

Diastereomeric excesses of up to 98% were obtained with *tert*-butyl-2-phenylcyclohexylmaleate **1a** but unfortunately only moderate stereoselectivity with the more readily available maleates **1b–c** derived from menthol or borneol (8 and 13% d.e., respectively). Tanaka et al.[8] reported recently good results in the diastereoselective Diels–Alder reaction of maleate **1d** derived from



1a-d



2-3a,b

1a : R_1 = *t*-Bu ; R_2 = 2-phenylcyclohexyl
1b : R_1 = *t*-Bu ; R_2 = menthyl
1c : R_1 = *t*-Bu ; R_2 = bornyl
1d : R_1 = Me ; R_2 = 8'-hydroxyl-1,1'-binaphthalene-8-yl

2 : R_1 = alkyl ; R_2 = chiral substituent
3a : R_1 = *n*-Bu ; R_2 = Me
3b : R_1 = 4-methyl-3-pentenyl ; R_2 = Me

Figure 1.

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PII: S0957-4166(02)00194-5

8,8′-BINOL. The introduction of a chiral sulfoxide substituent on an unsymmetrical maleate (2-sulfinylmaleate) is an alternative way to induce asymmetry but the *endo*/*exo* ratio of the adducts is often lower than with simple maleates, and depends largely on the temperature and the catalyst employed.[9,10]

To the best of our knowledge, the asymmetric Diels–Alder reaction of the chiral 2-alkyl substituted maleate **2** with cyclopentadiene has never been reported. In the course of our studies into the preparation of bicyclo[2.2.1]heptane natural products, we found that in the presence of organoaluminium catalysts, 2-butyl- and 2-(4-methyl-3-pentenyl) dimethyl maleates **3a** and **3b** reacted with cyclopentadiene at −78°C to afford the *endo* adduct quantitatively. The synthetic potential of the asymmetric version of this transformation was then explored, and we propose herein an application to the enantioselective synthesis of β-santalene.

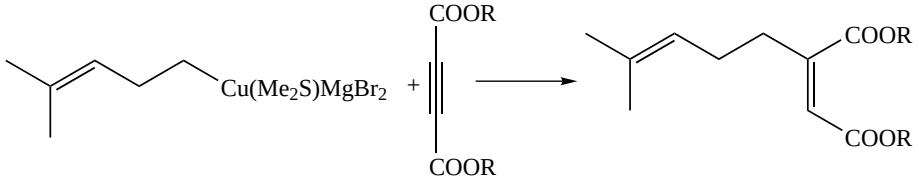
2. Results and discussion

We could efficiently prepare several 2-substituted maleates by addition of organocopper–dimethylsulfide complexes to various acetylenedicarboxylates.[11] The addition of butylcopper- and 4-methyl-3-pentenylcopper-dimethylsulfide complexes on dimethyl acetylenedicarboxylate proceeded in quantitative yields, but the choice of the alkyl halide as starting material for the generation of the copper reagent proved to be crucial. For instance, the butylcopper complex prepared from butylmagnesium iodide and $CuBr,Me_2S$ gave poor results compared to those obtained from butylmagnesium bromide. As our goal was to use chiral 2-substituted maleates, we carried out the addition of the 4-methyl-3-pentenylcopper-dimethylsulfide complex to bulky chiral acetylenedicarboxylate esters such as bis-(−)-menthyl-, bis-(+)-isomenthyl-, and bis-(+)-neomenthyl acetylenedicarboxylates **4a**, **4b** and **4c**, respectively. The desired chiral maleates **2a**, **2b** and **2c** were obtained in excellent yields (Scheme 1).

The Lewis acid-catalyzed Diels–Alder reaction of **2a** with cyclopentadiene was then investigated. The best results were obtained with 2 equiv. of Et_2AlCl or $EtAlCl_2$ at low temperature. Using the same conditions, the addition was incomplete using trimethylaluminium and not effective at all with $TiCl_4$, $SnCl_4$, BF_3Et_2O and BCl_3. Two diastereomeric adducts **5a** and **6a** were obtained in a 69/31 ratio (estimated by ^1H NMR). Experiments carried out at −78, −43 and −30°C showed that the temperature of the reaction had no significant influence on this ratio and unfortunately, the use of dienophiles derived from other readily available chiral auxiliaries **2b** and **2c** also led to a mixture of diastereomers in approximatively the same proportions (Scheme 2).

Diastereomers **5a** and **6a** could be separated by column chromatography, and the major one **5a** was thus isolated in 61% yield from **2a**. This product then could be used as an intermediate in the synthesis of enantiomerically pure β-santalene (Scheme 3).

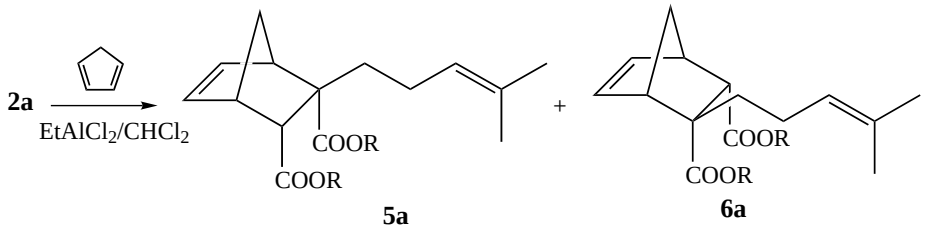
Reduction of this adduct with lithium aluminium hydride afforded the dextrorotatory form of diol **7** in 84% yield. As expected, the same treatment applied to compound **6a** led to the antipodal isomer (−)-**7**. Selective hydrogenation of the intracyclic double bond of (+)-**7** with nickel-P2[12] led quantitatively to **8**, which was subsequently treated with mesyl chloride in the presence



4a : R= menthyl
4b : R= isomenthyl
4c : R= neomenthyl

2a : R= menthyl
2b : R= isomenthyl
2c : R= neomenthyl

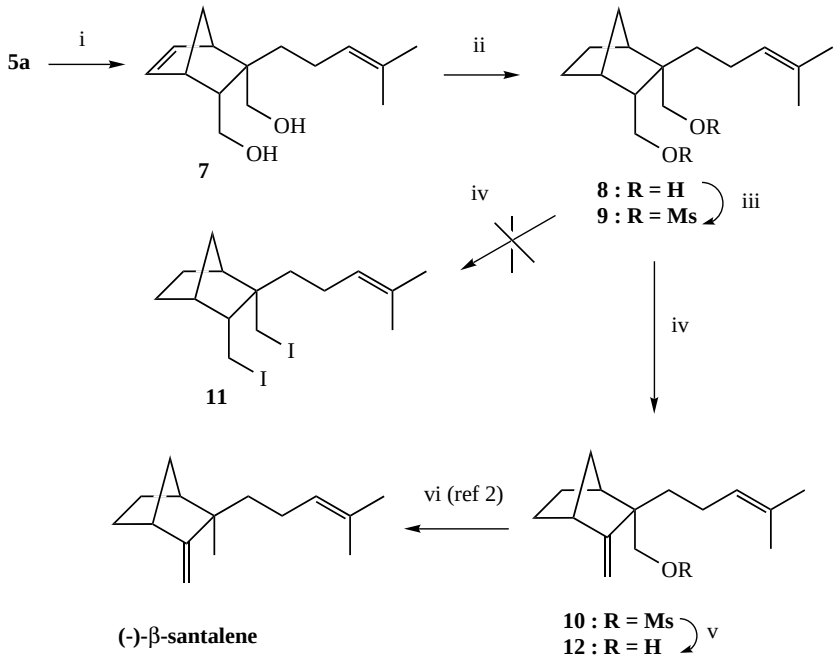
Scheme 1.



5a **6a**

R = Menthyl

Scheme 2.



Scheme 3. *Reagents*: (i) LAH, THF; (ii) Ni-P2, H_2, EtOH; (iii) MsCl, Et_3N, $CHCl_2$; (iv) NaI, HMPA, 122°C; (v) LAH, THF, reflux; (vi) (a) PCC, CH_2Cl_2, (b) NH_2NH_2, KOH ethylene glycol, reflux.

of triethylamine to afford the dimesylate **9**. Several attempts were made to prepare the monomesylate **10** by classical elimination methods. At best, the use of 10 equiv. of DBU in refluxing toluene for 24 h gave **10** in 39% yield, together with unreacted **9** and the application of longer reaction times decreased the yield with degradation products. However, in an attempt to prepare the diiodide **11** by treatment of **9** with sodium iodide in HMPA, the monomesylate **10** was obtained as the sole product in 42% yield after 1 h 45 min at 120°C, with no detectable amount of di- or monoiodide. This yield could be improved to 74% with the use of caesium carbonate. Unfortunately, all our attempts to reduce this product directly to β-santalene were unsuccessful: the use of lithium aluminium hydride led not surprisingly[13] to the alcohol **12** by hydride attack on the sulfur atom and even lithium triethylborohydride in toluene gave unwanted results. The reduction of **10** to **12** was indeed optimized to 94%. A 70% overall yield was finally obtained from dimesylate **9**. In a previous work[2] this alcohol had been already transformed to (−)-β-santalene (the natural enantiomer) in a two-step procedure: PCC oxidation to the aldehyde and Wolff–Kishner reduction in 72% overall yield. We were pleased to find that the specific rotation value of our product was in perfect agreement with the reported data.[2] The method described herein thus allows the preparation of (−)-β-santalene starting from readily accessible compounds.

3. Conclusion

In conclusion, we have developed a new procedure for formal synthesis of enantiomerically pure (−)-β-santalene, based on the asymmetric Diels–Alder addition of a chiral 2-substituted symmetrical maleate. This reaction shows moderate diastereoselectivity but uses a very inexpensive chiral auxiliary and separation of the minor diastereomer is easy. The described procedure allowed the preparation of the (−)-β-santalene precursor **12** in 96% e.e.

4. Experimental

4.1. General

According to the literature procedure, 5-bromo-2-methyl-2-pentene[14] was obtained from cyclopropylmethylketone in 67% yield and bis-(−)-menthyl acetylenedicarboxylate **4a** could be prepared in four steps and 66% overall yield[15] from the commercially available and inexpensive acetylene dicarboxylic monopotassium salt. This last method was also applied to the preparation of diisomenthyl- and dineomenthyl acetylenedicarboxylates **4b** and **4c**.

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer at 200 and 50 MHz, respectively. Chemical shifts were in ppm relative to solvent signal (residual proton signal for proton spectra or carbon signal for carbon spectra). IR spectra: Perkin–Elmer 257 spectrophotometer in cm^{-1}. Optical rotations: Perkin–Elmer 241 MC polarimeter between 20 and 25°C. Analytical TLC: precoated Merck silica gel 60F-254 glass plates; detection by UV (=254 or 365 nm) and/or visualization by spray reagents (ethanolic vanillin/H_2SO_4, *p*-anisaldehyde/H_2SO_4 or phosphomolybdic acid) or iodine. Preparative (column) chromatography: silica gel Geduran Si 60 (40–63 m; 70–230 mesh) from E. Merck. Work-up: organic solutions were

dried using magnesium sulfate monohydrate ($MgSO_4 \cdot H_2O$), filtered and concentrated by rotary evaporation at water aspirator pressure.

4.2. Bis-(−)-menthyl 2-(4-methyl-3-pentenyl)maleate 2a

To a suspension of $CuBr(Me_2S)$ (11.8 g, 57.4 mmol) in anhydrous THF (350 mL) was added dropwise at −78°C, a solution of Grignard reagent (55.08 g, 1.0 mmol/g) prepared from 5-bromo-2-methyl-2-pentene. The mixture was stirred during 40 min at −78°C and a solution of **4a** (16.4 g, 42 mmol) in THF (90 mL) was added slowly and stirred for 4 h at the same temperature. The mixture was then treated with 400 mL of a saturated aqueous NH_4Cl solution. After decantation, the aqueous phase was extracted and the resulting green oil was chromatographed on silica gel to give **2a** as a colorless solid (19.4 g, 97%). $[\alpha]_D^{25}$ −94 (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 1718, 1726, 2930, 2953 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.74 (1H, t, $J=1.5$ Hz), 5.09 (1H, bt, $J=7$ Hz), 4.6–4.9 (2H, m), 1.69 (3H, s), 1.60 (3H, s), 0.82–2.4 (22H, m), 0.92 (3H, d, $J=6$ Hz), 0.89 (9H, d, $J=6$ Hz), 0.80 (3H, d, $J=6.7$ Hz), 0.75 (3H, d, $J=7$ Hz); ^{13}C NMR ($CDCl_3$) δ: 16.03, 16.40, 17.71, 20.85, 20.97, 22.08, 23.20, 23.48, 25.69, 25.84, 25.89, 26.14, 31.45, 31.47, 34.36, 34.74, 40.38, 40.90, 47.10, 74.46, 75.34, 119.53, 122.35, 133.18, 150.13, 164.40, 168.46.

4.3. Bis-(−)-menthyl (1*S*,2*S*,3*R*)-2-(4-methyl-3-pentenyl)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate 5a

To a solution of **2a** (2.31 g, 4.87 mmol) in dichloromethane (60 mL) was added at −78°C a solution 1 M of diethylaluminium chloride in toluene (10 mL, 2 equiv.) followed after 15 min by cyclopentadiene (7 mL, 86 mmol). The resulting mixture was then stored at −30°C during 14 h and poured into a mixture of 1N HCl and ice. The cloudy solution was extracted with ether, the organic phases were washed with water, $NaHCO_3$ solution and brine, and then dried with $MgSO_4$. After evaporation of the solvent, the crude mixture of **5a** and **6a** was chromatographed on silica gel to afford pure diasteromer **5a** (1.60 g, 61%). $[\alpha]_D^{25}$ −114 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 1736, 2954, 2869 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.55 (1H, dd, $J=3.0$, 5.7 Hz), 5.93 (1H, dd, $J=3.0$, 5.7 Hz), 5.08 (1H, bt, $J=7$ Hz), 4.4–4.6 (2H, m), 3.04 (1H, bs), 2.79 (1H, bs), 2.69 (1H, d, $J=1$ Hz), 1.69 (3H, s), 1.62 (3H, s), 0.70–2.2 (24H, m), 0.70–0.92 (6×3H, 6×d); ^{13}C NMR ($CDCl_3$) δ: 15.87, 17.87, 21.13, 21.28, 22.16, 22.89, 25.18, 25.75, 31.41, 34.43, 40.82, 41.08, 41.67, 46.13, 46.74, 46.96, 47.07, 53.71, 54.71, 60.44, 74.41, 74.45, 124.38, 131.64, 133.14, 138.63, 172.51, 173.03. Anal. calcd for $C_{35}H_{56}O_4$: C, 77.73; H, 10.44. Found: C, 77.61; H, 10.58%.

4.4. (1*S*,2*S*,3*R*)-(4-Methyl-3-pentenyl)-2,3-bis(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (+)-7

A solution of **5a** (3.15 g, 5.83 mmol) in diethyl ether (10 mL) was added dropwise at room temperature to a suspension of $LiAlH_4$ (1.0 g, 26.3 mmol) in diethyl ether (50 mL) and stirred overnight. The mixture was then quenched with water and filtered. After evaporation, the crude mixture of **7** and menthol was separated by column chromatography to give pure compound **7** as a colorless oil (1.16 g, 84%). $[\alpha]_D^{25}$ +21 (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) 3306, 2866, 1460, 1039, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.07 (2H, bs), 5.16 (1H, bt, $J=6.72$ Hz), 3.3–3.7 (4H, m), 2.79 (2H, bs), 2.69 (1H, bs), 2.65 (1H, bs), 1.85–2.15 (3H, m), 1.69 (3H, s), 1.64 (3H, s), 1.14–1.6 (5H, m); ^{13}C NMR ($CDCl_3$) δ: 17.71, 23.22, 25.72, 38.80, 46.35, 47.23, 49.10, 49.81, 53.46, 63.77, 64.35, 124.99, 131.50, 134.61, 136.27.

4.5. (1*S*,2*S*,3*R*)-2,3-Bis(hydroxymethyl)-2-(4-methyl-3-pentenyl)bicyclo[2.2.1]heptane (+)-8

To a solution of (+)-**7** (0.884 g, 3.75 mmol), and $Ni(OAc)_2$ (0.14 g, 0.8 mmol) in 95% ethanol (25 mL) was added in one portion a solution of $NaBH_4$ (22.4 mg, 0.59 mmol) and NaOH (1.5 mg, 0.03 mmol) in aqueous ethanol (12 mL). The reaction flask was purged with hydrogen and stirred at room temperature for 1.5 h. The reaction mixture was then poured into 1N HCl and the mixture extracted with diethyl ether. The organic phases were washed with brine, dried ($MgSO_4$) and evaporated to afford **8** as a colorless oil which crystallized upon standing (0.873 g, 98%). $[\alpha]_D^{25}$ +26 (*c* 1.18, $CHCl_3$); IR ($CHCl_3$) 3294, 2953 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.14 (1H, bt, $J=7$ Hz), 3.5–4.0 (4H, m), 2.17 (2H, bs), 1.9–2.1 (2H, m), 1.69 (3H, s), 1.63 (3H, s), 1.1–1.6 (11H, m); ^{13}C NMR ($CDCl_3$) δ: 17.68, 21.68, 23.11, 23.55, 25.70, 37.59, 39.07, 40.79, 43.94, 44.77, 53.23, 61.98, 62.80, 125.07, 131.35. Anal. calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.35; H, 11.35%.

4.6. (1*S*,2*S*,3*R*)-2-(4-Methyl-3-pentenyl)bicyclo[2.2.1]-heptane-2,3-bis(methylmethane sulfonate) 9

To a solution of diol **8** (2.5 g, 10.50 mmol) and triethylamine (3.17 g, 31.3 mmol) in dichloromethane (130 mL) was added dropwise at 0°C mesyl chloride (3.688 g, 32.2 mmol). The mixture was then stirred for 2.5 h at room temperature and quenched by pouring into a mixture of HCl (1N) and ice, and extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to give a crude oil which was purified by column chromatography to afford **9** as a white solid (3.61 g, 87%). $[\alpha]_D^{25}$ −13 (*c* 2.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 5.08 (1H, bt, $J=6$ Hz), 4.1–4.3 (4H, m), 3.04 (3H, s), 3.02 (3H, s), 2.39 (1H, bs), 2.16 (1H, bs), 1.99 (2H, dt, $J=8.5$ Hz), 1.69 (3H, s), 1.63 (3H, s), 1.3–1.7 (9H, m); ^{13}C NMR ($CDCl_3$) δ: 17.65, 20.91, 22.14, 24.10, 25.67, 37.07, 37.18, 37.38, 37.68, 39.73, 44.05, 45.14, 48.43, 67.29, 68.49, 123.67, 132.12. Anal. calcd for $C_{17}H_{30}O_6S_2$: C, 51.75; H, 7.66; S, 16.25. Found: C, 51.77; H, 7.81; S, 16.43%.

4.7. (1*S*,2*S*)-3-Methylidene-2-(4-methyl-3-pentenyl)-bicyclo[2.2.1]heptane-2-methyl methanesulfonate 10

Compound **9** (47.7 mg, 0.12 mmol) was dissolved in dry HMPA (1.5 mL) with sodium iodide (187 mg, 1.25 mmol) and caesium carbonate (50 mg, 0.26 mmol). The mixture was heated in an oil bath at 122°C for 1.25 h, poured into cold brine and extracted with ethyl acetate. After purification by column chromatography, monomesylate **10** was obtained as a colorless oil (26.6 mg, 74%). $[\alpha]_D^{25}$ −64 (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 5.08 (1H, bt, $J=7$ Hz), 4.90 (1H, s), 4.57 (1H, s), (2H, AB, $J_{AB}=9.5$ Hz, $\nu_A=4.21$, $\nu_B=4$), 3.02 (3H, s), 2.71 (1H, bd), 2.28 (1H, bs), 1.9–2.16 (2H, m), 1.68 (3H, s), 1.61 (3H, s), 1.2–1.8 (8H, m); ^{13}C NMR ($CDCl_3$) δ: 17.65, 23.04, 23.55, 25.72, 29.81, 35.80, 36.85, 37.18, 43.93, 46.63, 48.10, 72.46, 103.81, 124.14, 131.83, 159.39. Anal. calcd for $C_{16}H_{26}O_3S$: C, 64.39; H, 8.78; S, 10.74. Found: C, 64.38; H, 8.90; S, 10.88%.

4.8. (1*S*,2*S*)-3-Methylidene-2-(4-methyl-3-pentenyl)-bicyclo[2.2.1]heptane-2-methanol 12

To a solution of **10** (104 mg, 0.35 mmol) in THF (7 mL) was added lithium aluminium hydride (75 mg, 2 mmol). The mixture was heated under reflux for 30 min and quenched at 0°C with water, filtered, evaporated and chromatographed to afford alcohol **12** (72 mg, 94%). $[\alpha]_D^{23}$ −127 (*c* 0.7, EtOH) [lit.:[2] $[\alpha]_D^{23}$ −129 (*c* 0.7, EtOH)].

Acknowledgements

We thank the Collectivité Territoriale de Corse (CTC) for financial support in the form of a fellowship.

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