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Diastereoselective addition of monoterpenic alcoholates and thiolates to 2,3-dicarbomethoxynorbornadiene

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Abstract

Addition of excess lithium salts of (–)-menthol or (–)-borneol to 2,3-dicarbomethoxynorbornadiene **1** affords the transesterification–addition products **4** and **5**. The thiols derived from the same monoterpenes give only the addition products to the activated double bond, **6** and **7**. In all cases, the addition reaction is totally *exo*-selective with respect to the norbornadiene moiety and moderately selective in discriminating the *si*- and *re*-face of the double bond. Both diastereomeric products are formed as a mixture of *endo–exo* epimers at C3. The major addition product of (–)-menthol to **1** is crystalline, of known absolute configuration, and has potential as a precursor of chiral ligands. © 2000 Published by Elsevier Science Ltd.

1. Introduction

Desymmetrization of a *meso* compound is nowadays well recognized as a convenient method for performing asymmetric synthesis.[1] The clear advantage of this synthetic strategy is that, in principle, the yields of the desired enantiomer are quantitative, without waste of material due to the unwanted enantiomer. Furthermore, avoiding formation of the wrong enantiomer, allows reduced environmental impact. Following the development of different desymmetrization protocols for disubstituted polycyclic alkenes, we then considered the reaction of 2,3-dicarbomethoxynorbornadiene **1** with monoterpenic alcoholates and thiolates. In some respects, this reaction is similar to the recently reported desymmetrization of 2,3-bis(phenylsulfonyl)norbornadiene that has been shown to be quite efficient in terms of yields and diastereoselectivity.[2] From another point of view, it represents an extension to the recently reported desymmetrization of related polycyclic succinates.[3] As shown in Scheme 1, at the outset, three alternative pathways were considered as possible outcomes of the reaction: addition, transesterification and transesterification–addition. This study concerns the products of addition of nucleophiles to the electron-poor double bond rather than the transesterification reactions.[4]

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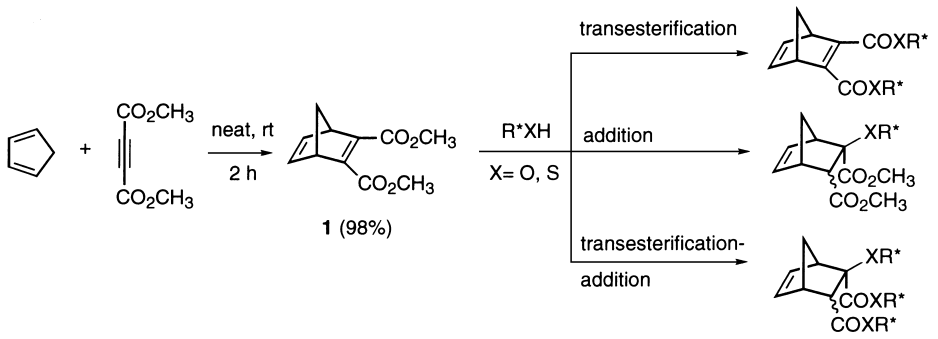
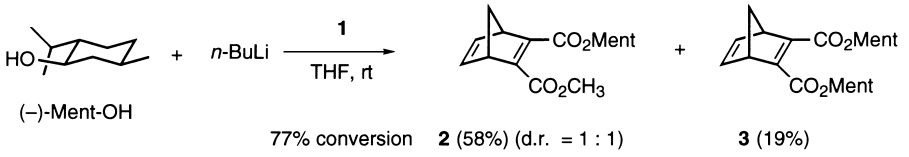


Scheme 1.

2. Results and discussion

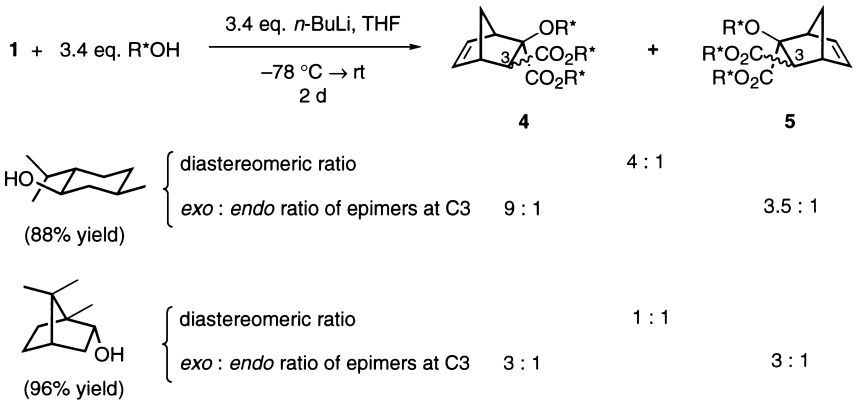
2,3-Dicarbomethoxynorbornadiene **1** is readily available by the reaction of dimethyl acetylene dicarboxylate with cyclopentadiene. At slight variance with the reported reaction conditions (silica gel, CH_2Cl_2, 24 h, 80%),[5] it was observed that the desired cycloadduct **1** is obtained in 98% yield simply by mixing the two components neat at room temperature for 2 h. When an equimolar ratio of lithium mentholate (as obtained from (–)-menthol and *n*-BuLi in THF at –78°C)[3,6] and **1** was mixed in THF at rt, a 77% conversion to the mono and ditransesterified products **2** (58% yield) and **3** (19% yield) was obtained (Eq. (1)). This observation shows that nucleophilic attack of the 'hard' mentholate occurs on the 'hard' carboxy group rather than the 'soft' alkenyl carbon. The monosubstituted product **2** is a 1:1 mixture of diastereoisomers. Other bases and different anions afford crude reaction mixtures contaminated with a number of side products that were not further studied.



(1)

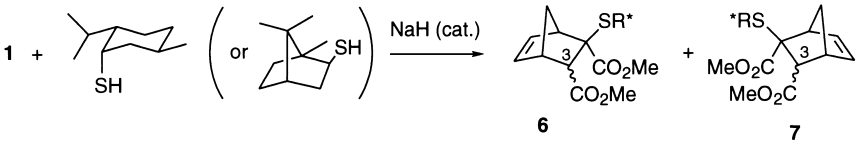
On using an excess of lithium mentholate or on performing the reaction directly onto the dimonoterpenic ester (**3** in the case of menthol) a slow reaction occurs leading to a mixture of four diasteromeric products in 88% yield. They were separated into two fractions and identified as the products of a selective *exo* attack of the nucleophile on the *si* and *re* face of **1**. Each fraction contains **4** and **5** as a mixture of *exo–endo* epimers at C3 in yields and ratio as represented in Scheme 2 below. The reaction with (–)-borneol leads to comparable results (Scheme 2).

With the aim of improving the diastereoselectivity of the Michael addition, the reaction was carried out at low temperature or with concave-type alcohols of known higher performances[7] (i.e. 8-phenylmenthol and 2-phenylcyclohexanol). In both cases, however, the addition reactions proved too long for practical application. On searching for more reactive nucleophiles, the thiols derived from menthol[8] and borneol[9] were considered. The reactions with both these compounds give the opportunity to investigate either the effect of the thiol function on the diastereoselectivity



Scheme 2.

of the addition reaction and the effect of the different configuration of the carbon atom containing the functional group. Treatment of **1** with the thiolates (which may be generated with *n*-BuLi as before or better with catalytic NaH) affords the Michael addition products **6** and **7** in the yields and ratios shown in Scheme 3 and Table 1.



Scheme 3.

Table 1

R*SH	Solvent	Temp. (°C)	t (h)	Yield (%)	**6 : 7**[a]
(+)-neomenthanethiol	toluene	25	2	92	1 : 2
(1*S*-*exo*)-2-bornanethiol	toluene	25	2	98	1 : 2
(1*S*-*exo*)-2-bornanethiol	THF	25	2	98	1 : 0.6
(1*S*-*exo*)-2-bornanethiol	THF	–78	5.5	98	1 : 4.5
(1*S*-*exo*)-2-bornanethiol	toluene	–78	7	90	1 : 2.5

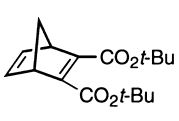
[a]Absolute configuration unknown. Variable mixture of epimers at the C3.

As expected on the basis of 'hard–soft' considerations, the reaction is highly chemoselective affording the Michael addition products only and significantly faster than with the corresponding alcohols. At room temperature, it takes ca. 2 h to reach completion and affords with either thiols a 2:1 mixture of diastereoisomers **6** and **7** (as a mixture of epimers at C3 as represented). A quite different ratio was observed on changing the solvent from toluene to the more coordinating THF. In this case, carrying out the reaction at room temperature, the diastereoisomeric ratio is

reversed, i.e. the major isomer becomes the minor and vice versa. Very unexpectedly, the ratio changes highly in favor of the former isomer on lowering the temperature to –78°C. No such a dramatic temperature effect is observed in toluene.

With the aim of gaining more information regarding the steric hindrance of the reaction and in order to broaden the scope of the substrates, compounds **8**–**10**[10] were investigated. As reported in Table 2, although the reactions with **8** and **9** occur in high yields, the diastereoselectivity is in all cases poor, suggesting that the steric hindrance of the reacting ester is not important for the diastereoselectivity of the reaction. The reactivity of the imide **9** appeared quite inferior with respect to **1** and **8** and no reaction was observed under these conditions for the anhydride **10**.

Table 2



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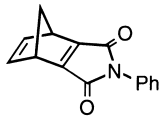

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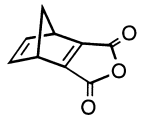
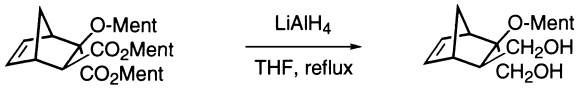


10

Substrate	R*SH	Solvent	Temp. (°C)	Yield (%)	d.r.
8	(1*S*-*exo*)-2-bornanethiol	toluene	0	98	1 : 1
8	(1*S*-*exo*)-2-bornanethiol	THF	–78	98	1 : 2
9	(1*S*-*exo*)-2-bornanethiol	toluene	25	95	1 : 1
10	(1*S*-*exo*)-2-bornanethiol	toluene	25	-	-

In the case of the addition of lithium (–)-mentholate to **1**, the crude reaction mixture was recrystallized from hot MeOH. The large crystals of the diastereomerically (enantiomerically) pure major product **4** (*exo* at C3) which were obtained in 52% yield were analyzed by X-ray diffractometry[11] to prove the absolute configuration assigned in the drawing of Scheme 1 and in Eq. (2). Because of the large amount of this compound which can be obtained with very little effort, we thought to transform *exo*-6 into the corresponding diol which, as shown for other cases in the literature,[12] is potentially a quite effective chiral ligand for catalysts to be used in asymmetric synthesis. Reduction with lithium aluminium hydride in refluxing THF affords compounds **11** in close to quantitative yield. The latter is similar to other diols recently employed in asymmetric synthesis with the same aim.[13]



exo-**4** **11** (2)

It should be noticed that despite the fair selectivity, the low cost of the reagents and the ease of the operations make this reaction a valuable method for the obtainment of enantiopure polyfunctionalized molecules that can be valuable intermediates in the synthesis of many natural or bioactive compounds.[14]

3. Experimental

3.1. 2,3-Dicarbomethoxynorbornadiene *1*

Freshly distilled dimethyl acetylenedicarboxylate (5.5 mL, 44.7 mmol) was added dropwise to freshly distilled cyclopentadiene (2.95 g, 44.7 mmol), cooling the mixture with a water bath when the temperature exceeded 45°C. The mixture was stirred for an additional 2 h. The resulting 9.3 g (quantitative yield) of colorless oil was pure by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 6.91 (1H, t, $J=1.9$ Hz), 3.93 (1H, m), 3.77 (6H, s), 2.27 (1H, dt, 1/2 AB, $J=6.7$ and 1.5 Hz), 2.09 (1H, dt, 1/2 AB, $J=6.7$ and 1.5 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 164.8, 152.0, 142.0, 72.6, 53.1, 51.4. IR (film) 1714 (CO) cm^{-1}.

3.1.1. Addition of 1 equivalent of mentholate to *1*

To a solution of (–)-menthol (780 mg, 5.0 mmol) in dry THF (5 mL), maintained at –78°C under an argon atmosphere, was added via syringe a solution of *n*-BuLi in hexane (2.5 M, 2.0 mL, 5.0 mmol). The mixture was warmed to 0°C and maintained at the same temperature for 15 min. Dicarbomethoxynorbornadiene **1** (1.0 g, 5.0 mmol) was added and the resulting slurry was maintained under vigorous stirring at rt for 24 h. The resulting solution was poured into H_2O (40 mL) and was extracted with Et_2O (4×25 mL). Combined organic extracts were dried over $MgSO_4$, concentrated in vacuum and purified by flash chromatography (eluant CH_2Cl_2:hexanes 1:1). First eluate: 310 mg (yield: 14%) of bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxydi-(1*R*-(2*S*-isopropyl-5*R*-methylcyclohexyl)) **3** as a colorless solid, mp 107–109°C. $[\alpha]_D^{25}=-86.6$ ($c=1.6$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 6.91 (1H, m), 4.78 (1H, m, $J=10.8$ and 4.4 Hz), 3.89 (1H, bs), 2.30 (1H, m), 2.16–0.73 (37H, series of m). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 164.9, 142.6, 142.2, 74.8, 72.6, 53.6, 53.2, 46.8, 46.7, 40.7, 40.7, 34.2, 31.3, 26.1, 23.4, 22.0, 20.6, 16.1. IR (KBr) 1733, 1704 (CO) cm^{-1}. Anal. calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.08; H, 9.73. Second eluate: 697 mg (yield: 42%) of colorless oil bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxymethyl-(1*R*-(2*S*-isopropyl-5*R*-methylcyclohexyl)) **2** as a mixture of diastereoisomers in 1:1 ratio. ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 6.97–6.88 (4H, m), 4.80 (1H, dt, $J=10.8$ and 4.4 Hz), 3.98–3.88 (4H, m), 3.76 (6H, s), 2.33–2.26 (1H, series of m), 2.13–1.99 (6H, series of m), 1.99–0.95 (14H, series of m), 0.92 (6H, d, $J=6.5$ Hz), 0.91 (6H, d, $J=7.0$ Hz), 0.79 (3H, d, $J=7.0$ Hz), 0.78 (3H, d, $J=7.0$ Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 166.6 (2C), 164.8 (2C), 142.5, 142.3 (2C), 142.1, 74.9 (2C), 72.8, 72.5, 53.6, 53.4, 53.2, 53.1, 51.71 (2C), 46.9 (2C), 40.7, 40.6, 34.1 (2C), 31.3 (2C), 26.0 (2C), 23.4, 23.3, 21.89 (2C), 20.7, 20.6, 16.2 (2C). IR (KBr) 1729, 1703, 1618 (CO) cm^{-1}. Anal. calcd for $C_{20}H_{29}O_4$: C, 72.04; H, 8.77. Found: C, 71.88; H, 8.79. Third eluate: 170 mg of **1** as a colorless oil identical to authentic sample.

3.1.2. Addition of 2 equivalents of mentholate to *1*

To a solution of (–)-menthol (625 mg, 5.0 mmol) in dry THF (4 mL), maintained at –78°C under an argon atmosphere, was added via syringe a solution of *n*-BuLi in hexane (2.5 M, 1.6 mL, 4.0 mmol). The mixture was warmed to 0°C and maintained at the same temperature for 15 min. Dicarbomethoxynorbornadiene **1** (415 mg, 2.0 mmol) was added and the resulting slurry was maintained under vigorous stirring at rt for 24 h. After the usual work-up, **3** (identical to authentic sample) was obtained in 94% yield without further purifications.

*3.1.3. Addition of excess of mentholate to **1***

To a solution of (–)-menthol (2.66 g, 17.0 mmol) in dry THF (17 mL), maintained at –78°C under an argon atmosphere, was added via syringe a solution of *n*-BuLi in hexane (2.5 M, 6.8 mL, 17.0 mmol). The mixture was warmed to 0°C and maintained at the same temperature for 15 min. Dicarbomethoxynorbornadiene **1** (1.04 g, 5.0 mmol) was added and the resulting slurry was maintained under vigorous stirring at rt for 48 h. After usual work-up the crude was recrystallized from hot methanol to afford 1.60 g (52% yield) of (2*R*,3*S*)-2*exo*-[1*R*-(2*S*-isopropyl-5*R*-methylcyclohexyloxy)]-2*endo*,3*exo*-di{carboxy-[1*R*-(2*S*-isopropyl-5*R*-methylcyclohexyl)]}bicyclo-[2.2.1]hept-5-ene *exo*-**4**, as colorless prisms, mp 151–152°C. $[\alpha]_D^{25} = -14.0$ ($c = 1.5$, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 6.21 (1H, dd, $J = 5.5$ and 2.9 Hz), 6.13 (1H, dd, $J = 5.5$ and 3.0 Hz), 4.77–4.47 (1H, series of m), 3.58 (1H, m, $J = 9.9$ and 3.8 Hz), 3.25 (1H, bs), 2.92 (1H, bs), 2.75 (1H, d, $J = 2.2$ Hz), 2.36–.83 (9H, series of m), 1.80–1.22 (16H, series of m), 1.21–1.01 (6H, series of m), 1.01–0.68 (27H, series of d). ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 172.9, 171.1, 139.0, 136.8, 87.8, 75.0, 74.2, 73.5, 54.7, 48.7, 47.1, 47.0, 46.1, 45.7, 43.8, 41.1, 40.9, 40.0, 34.5 (2C), 34.2, 31.5, 31.2 (2C), 26.2, 24.8, 24.1, 23.5, 22.6, 22.6, 22.2, 22.1, 21.9, 21.4 (2C), 20.7, 16.5, 16.0, 15.6. IR (KBr) 1727, 1716 (CO) cm^{-1}. Anal. calcd for $C_{20}H_{29}O_4$: C, 72.04; H, 8.77. Found: C, 71.88; H, 8.79. Concentration and purification of the mother liquors by flash chromatography (eluant CH_2Cl_2:hexanes, 1:1) afforded 456 mg (20% yield) of **3** identical to an authentic sample and 340 mg (11% yield) of a mixture of diastereomers **4** and **5** that was not further elaborated.

3.1.4. Reduction of exo-***4***

To a suspension of $LiAlH_4$ (200 mg, 5.3 mmol) in dry THF (1 mL), under an argon atmosphere at 0°C, was added dropwise a solution of *exo*-**4** (500 mg, 0.8 mmol) in dry THF (5 mL). The mixture was stirred for 1 h at rt and 1 h at reflux. The mixture was cooled in an ice bath and H_2O (5 mL) was added dropwise. The resulting slurry was poured into 1 M HCl (10 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuum and purified by flash chromatography (eluant CH_2Cl_2, then Et_2O) and recrystallization from hot hexanes to afford 220 mg (yield: 87%) of (2*R*,3*S*)-2*exo*-[1*R*-(2*S*-isopropyl-5*R*-methylcyclohexyloxy)]-2*endo*,3*exo*-dihydroxymethyl-bicyclo[2.2.1]hept-5-ene **11** as colorless prisms, mp 93–95°C. $[\alpha]_D^{25} = -58.4$ ($c = 2.5$, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 6.26 (1H, dd, $J = 5.6$ and 3.1 Hz), 6.01 (1H, dd, $J = 5.6$ and 3.1 Hz), 3.83 (1H, d, 1/2 AB, $J = 11.6$ Hz), 3.76–3.47 (3H, series of m), 3.24 (1H, d, 1/2 AB, $J = 11.6$ Hz), 2.95 (1H, bs), 2.49 (1H, bs), 2.36–2.16 (1H, series of m), 1.99 (1H, d, $J = 8.6$ Hz), 1.86–1.16 (7H, series of m), 1.12–0.96 (1H, series of m), 0.92 (6H, d, $J = 6.7$ Hz), 0.76 (3H, d, $J = 6.8$ Hz), alcoholic protons not observed. ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm): 140.0, 133.5, 88.0, 73.4, 67.9, 64.2, 50.6, 49.3, 46.8, 45.7, 43.8, 43.3, 34.1, 31.7, 25.0, 22.9, 22.3, 21.6, 15.8. IR (KBr) 3397 (OH) cm^{-1}. Anal. calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.82; H, 10.47.

*3.1.5. Addition of excess of borneolate to **1***

To a solution of (–)-borneol (1.08 g, 7.0 mmol) in dry THF (2 mL), maintained at –78°C under an argon atmosphere, was added via syringe a solution of *n*-BuLi in hexane (2.5 M, 2.8 mL, 7.0 mmol). The mixture was warmed to 0°C and maintained at the same temperature for 15 min. Dicarbomethoxynorbornadiene **1** (416 mg, 2.0 mmol) was added and the resulting slurry was maintained under vigorous stirring at rt for 48 h. After the usual work-up the crude was analyzed by ^1H NMR.

*3.1.6. General procedure of addition of thiolates to **1***

To a suspension of **1** (200 mg, 1.0 mmol), (+)-menthanethiol or (+)-bornanethiol (170 mg, 1.0 mmol) in dry toluene or THF (1 mL), maintained under argon, was added NaH (5 mg, 0.2 mmol). The slurry was stirred for the time reported in Table 1 at the indicated temperature. The resulting mixtures were poured in water (40 mL), extracted with Et_2O (3×25 mL), and the combined organic extracts dried over $MgSO_4$ and concentrated. The final crudes were analyzed by ^1H NMR.

Acknowledgements

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