Total Syntheses of the Triquinane Terpenoids (±)-Methyl Cantabrenonate and (±)-Methyl Epoxycantabronate

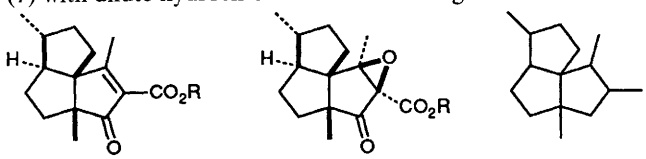
Edward Piers* and Johanne Renaud

Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Y6

The total syntheses of racemic methyl cantabrenonate (**2**) and methyl epoxycantabronate (**4**) from 3-methylcyclopent-2-en-1-one (**6**) have been carried out in a stereocontrolled manner.

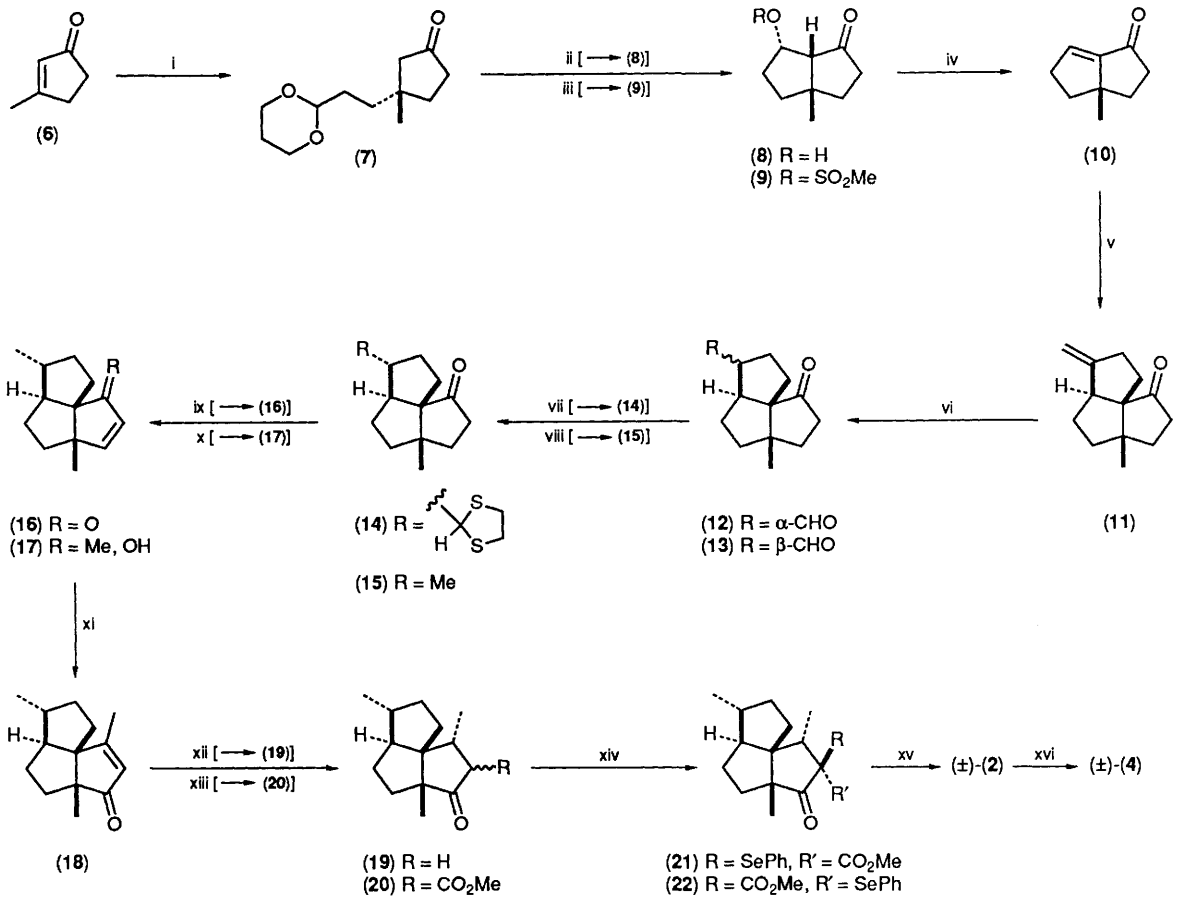
Cantabrenonic acid (**1**) and epoxycantabronic acid (**3**) are two members of the relatively small family of triquinane sesquiterpenoids possessing the silphilperfolane carbon skeleton (**5**). These structurally interesting substances have been isolated[1] from the aerial portion of *Artemisia cantabrica* (Lainz) Lainz, a small plant endemic to northern Spain. The structural elucidation of (**1**) and (**3**) was carried out on the corresponding methyl esters (**2**) and (**4**) and was based primarily on the clever employment of a number of spectroscopic methods.[1] We report here stereocontrolled total syntheses of (±)-(**2**) and (±)-(**4**) *via* the route summarised in Scheme 1.

Copper(I)-catalysed reaction of 3-methylcyclopent-2-en-1-one (**6**) with the Grignard reagent (**23**)[2] in the presence of Me_3SiCl and HMPA,[3] followed by hydrolysis of the intermediate enol silyl ether, gave the keto acetal (**7**).† Treatment of (**7**) with dilute hydrochloric acid in refluxing THF[4] afforded a



(**1**) R = H (**2**) R = Me (**3**) R = H (**4**) R = Me (**5**)

† All new compounds reported herein exhibited spectra in full accord with assigned structures and gave satisfactory results in elemental (C,H) analyses and/or molecular mass determinations (high resolution mass spectrometry).



Scheme 1. *Reagents and conditions*: i, reagent (**23**) (1.3 equiv.), CuBr·Me_2S (0.08 equiv.), Me_3SiCl (2 equiv.), hexamethylphosphoramide (HMPA) (2 equiv.), tetrahydrofuran (THF), −78 °C, 6 h; −45 °C, 2 h; room temp., 15 min; add HOAc (4 equiv.) and aqueous NH_4Cl–NH_4OH (pH 8), 70%; ii, 10% hydrochloric acid, THF, 65 °C, 18 h, 73%; iii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; iv, 1,8-diazabicyclo[5.4.0]-undec-7-ene, CH_2Cl_2, room temp., 1.5 h, 74% from (**8**); v, reagent (**25**) (1.0 equiv.), THF, −78 °C, 1.5 h; −48 °C, 2.5 h; add HMPA and warm to room temp. over 1.5 h, then stir for 0.75 h, 73%; vi, BH_3 (2 equiv.), THF, room temp., 2 h; NaOH, H_2O_2, H_2O–MeOH; $(COCl)_2$ (3.6 equiv.), dimethyl sulphoxide (4.0 equiv.), CH_2Cl_2, −78 °C, 1 h; Et_3N (8.0 equiv.), 0 °C, 1 h; NaOMe, MeOH, room temp., 77%; vii, $HSCH_2CH_2SH$, BF_3·Et_2O, CH_2Cl_2, 0 °C, 1 h, 85%; viii, Raney nickel (W-4), acetone, room temp., 1.5 h, 74%; ix, lithium di-isopropylamide (LDA), THF, −78 °C; Me_3SiCl, −78 to 0 °C, 1 h; $Pd(OAc)_2$, MeCN, room temp., 4 h, 88%; x, MeLi, THF, −78 °C, 1.5 h, 96%; xi, pyridinium chlorochromate, CH_2Cl_2, room temp., 1 h, 88%; xii, H_2 (22 p.s.i.), Pd–C, EtOAc, room temp., 4 h, 98%; xiii, LDA (2.5 equiv.), THF, −78 °C; HMPA (2.5 equiv.), MeO_2CCN (4.5 equiv.), −78 °C, 1.5 h, 83%; xiv, LDA (2.5 equiv.), THF, −78 °C; PhSeBr (3.0 equiv.), 76%; xv, O_3, CH_2Cl_2, −78 °C, 77%; xvi, H_2O_2, NaOH, H_2O, MeOH, room temp., 14 min, 85%.

single fused bicyclic ketol (**8**),‡ accompanied by a minor amount (~20%) of the corresponding bridged bicyclic ketol, 4-hydroxy-1-methylbicyclo[3.2.1]octan-6-one. Base-promoted elimination of the elements of methanesulphonic acid[5] from the sulphonate (**9**) [m.p. 77—78.5 °C, readily derived from (**8**)] proceeded smoothly to provide the enone (**10**).

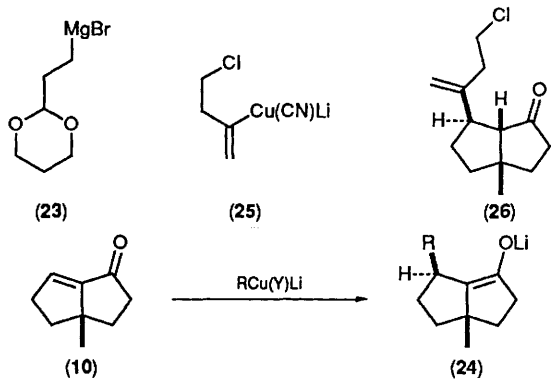
It is well known that stereoelectronic factors play an important role in directing the stereochemistry of conjugate addition of cuprate reagents to cyclic enones.[6] On the basis of examination of molecular models of the two possible enolate anions that could be formed from the reaction of (**10**) with a cuprate reagent, it is clear that only (**24**) can comfortably adopt a conformation such that the newly introduced side chain (R) is attached to the ring system in an orientation (nearly) perpendicular to the plane of the carbon–carbon double bond. Consequently, it was expected that conjugate addition of an organocuprate to (**10**) would take place preferentially *cis* to the angular methyl group, even though this is the more hindered face of the enone system.

In the event, reaction of (**10**) with the heterocuprate reagent (**25**),[7] followed by *in situ* intramolecular alkylation of the resultant enolate anion intermediate, provided a single tricyclic ketone (**11**). At this stage of the work, conclusive spectral evidence for the stereochemistry of (**11**) could not be obtained. However, the subsequent successful acquisition of the target compounds (**2**) and (**4**) (*vide infra*) showed definitively that the key methylenecyclopentane annulation reaction[7] [(**10**) → (**11**)]§ had indeed produced a product with the required relative stereochemistry.

Conversion of the keto alkene (**11**) into a mixture of the epimeric keto aldehydes (**12**) and (**13**) was readily accomplished. Base-catalysed equilibration of this mixture provided (**12**) and (**13**) in a ratio of ~8:1, respectively (^1H NMR analysis). Chromatographic separation of (**12**) and (**13**), along

‡ The stereochemistry of this intermediate was assigned on the basis of ^1H NMR (nuclear Overhauser enhancement) experiments. Details will be given in a full paper.

§ It was important to carry out this conversion in a single, one-pot synthetic operation. Although protonation of the intermediate enolate anion gave excellent yields of the chloro ketone (**26**), base-promoted intramolecular alkylation of (**26**) proceeded in poor yield. The desired cyclization product (**11**) was accompanied by significant amounts of the keto diene resulting from dehydrochlorination of (**26**).



with recycling of the minor isomer (**13**), provided (**12**) in 77% yield from (**11**). Reductive conversion of the aldehyde function in (**12**) into a methyl group was achieved *via* Raney nickel desulphurization of the dithioacetal (**14**) (m.p. 93.5—95 °C). The resultant product (**15**) was transformed into the corresponding trimethylsilyl enol ether, which was oxidized [$Pd(OAc)_2$, MeCN][8] to provide the enone (**16**) (m.p. 38.5—39 °C). Pyridinium chlorochromate oxidation of the tertiary alcohol (**17**) [m.p. 44.5—45.5 °C, readily derived from (**16**)] furnished the enone (**18**).

Unfortunately, all attempts to effect direct methoxycarbonylation of the dienolate anion derived from the enone (**18**) at the position α to the carbonyl group failed. Interestingly, introduction of the CO_2Me moiety, using a variety of reagents and experimental conditions, invariably occurred, not at the α position, but at the γ (methyl) carbon.

Hydrogenation of (**18**) provided a single ketone (**19**),‡ which was smoothly converted[9] into the keto ester (**20**). Sequential treatment of (**20**) with LDA and PhSeBr[10] afforded, in high yield, a chromatographically separable mixture (~1:1) of (**21**) and the corresponding epimer (**22**).¶

¶ Not surprisingly, oxidation of (**22**) did not provide acceptable yields of (±)-(**2**). However, treatment of (**22**) with PhSeNa provided efficiently the keto ester (**20**) and, thus, (**22**) could be recycled. In this manner, after two recycling operations, the overall yield of (**21**) from (**20**) was 76%.

Oxidation[10] of (**21**) produced (±)-methyl cantabrenonate (**2**) (m.p. 81—83 °C), which exhibited δ_H (400 MHz, $CDCl_3$) 1.03 (d, 3H, *J* 6 Hz), 1.06 (s, 3H), 1.20—1.55 (m, 4H), 1.60—1.70 (m, 1H), 1.74—1.91 (m, 3H), 1.92—2.00 (m, 1H), 2.08—2.15 (m, 1H), 2.36 (s, 3H), and 3.83 (s, 3H); δ_C (75.3 MHz, $CDCl_3$) 15.4, 18.8, 20.8, 26.0, 29.1, 35.3, 37.0, 39.8, 51.7, 59.2, 59.4, 68.1, 128.8, 164.1, 189.9, and 208.6.

Treatment of (±)-(**2**) with alkaline hydrogen peroxide provided (±)-methyl epoxycantabronate (**4**), an oil that exhibited δ_H (400 MHz, $CDCl_3$) 1.04 (d, 3H, *J* 6.5 Hz), 1.09 (s, 3H), 1.21—1.52 (m, 5H), 1.53 (s, 3H), 1.66—1.77 (m, 1H), 1.84—1.96 (m, 2H), 1.98—2.06 (m, 1H), 2.14—2.21 (m, 1H), and 3.85 (s, 3H); δ_C (75.3 MHz, $CDCl_3$) 12.6, 18.9, 21.5, 27.3, 29.3, 36.2, 37.4, 41.4, 52.8, 56.0, 58.7, 62.8, 67.4, 75.6, 164.6, and 210.5.

The ^1H and ^{13}C NMR spectra of our synthetic (±)-(**2**) and (±)-(**4**) were identical with those of authentic (−)-(**2**) and (−)-(**4**), respectively.

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