

Asymmetric Synthesis of Clerodane Diterpenoids: Total Synthesis of (–)-Methyl Kolavenate

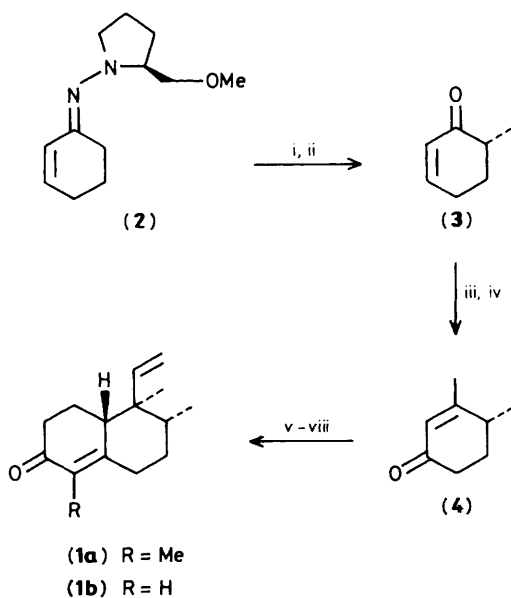
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The asymmetric synthesis of (8*R*,9*S*,10*R*)-4,8,9-trimethyl-9-vinyl- Δ^4 -3-octalone, a versatile intermediate for the syntheses of both *trans*- and *cis*-neo-clerodane diterpenoids, has been achieved by extension of Ender's asymmetric alkylation, and its utility is exemplified by the total synthesis of (–)-methyl kolavenate, the first example of a clerodane diterpenoid in optically active form.

The problem of the absolute configuration in clerodane diterpenoids was settled only recently by the reappraisal of physical methods,¹ while a chiral synthesis of a clerodane diterpenoid, which should corroborate the conclusion, has not been reported. We report here a method for the asymmetric synthesis of the Δ^4 -3-octalone intermediates (**1**), which are useful for the syntheses of both *trans*- and *cis*-clerodane diterpenoids,² and the total synthesis of (–)-methyl kolavenate utilizing this method.

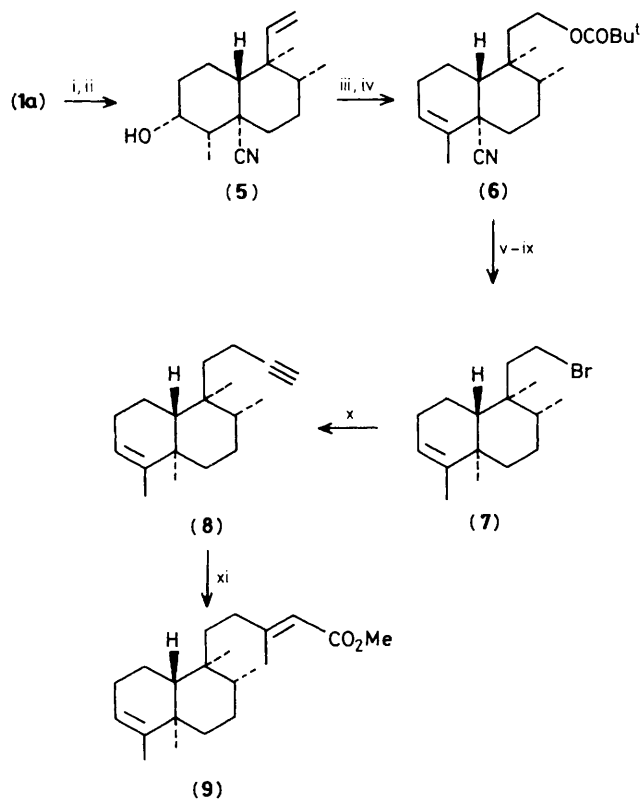
Since the octalone intermediates (**1**) are derivable from 3,4-dimethylcyclohex-2-enone (**4**),² our task amounts to the chiral preparation of the latter. We envisaged that (**4**) could be prepared from 6-methylcyclohex-2-enone (**3**), which, in turn, should be obtainable in both enantiomeric forms from cyclohex-2-enone by the application of Ender's asymmetric alkylation.³ The methylation of cyclohexenone (*S*)-amino-2-(methoxymethyl)pyrrolidine (SAMP)-hydrazone (**2**) with methyl iodide followed by acidic hydrolysis was reported to give (**3**) in optical yields of 61–75% enantiomeric excess (e.e.). Improvements of this method were first studied, and we found that the use of methyl toluene-*p*-sulphonate as the alkylating reagent dramatically increased the optical purity of the product. Thus the reaction of the lithiated hydrazone with methyl toluene-*p*-sulphonate in tetrahydrofuran (THF) initially at –95°C and then at up to –20°C afforded the



Scheme 1. Reagents: i, Pr^iNLi , THF, then *p*- $\text{MeC}_6\text{H}_4\text{SO}_3\text{Me}$; ii, MeI, then 2M HCl, pentane; iii, MeLi, Et_2O ; iv, PCC, CH_2Cl_2 ; v, $\text{CH}_2=\text{CHMgBr}\cdot(\text{Bu}^n_3\text{PCu})_4$, THF, then CH_2O ; vi, MeSO_2Cl , Et_3N , CH_2Cl_2 ; vii, $\text{EtCOCH}_2\text{CO}_2\text{Me}$, NaOMe, benzene; viii, 2M HCl, MeOH, reflux.

methylated product, which exhibits a ^1H n.m.r. methyl signal only at δ 1.06 corresponding to one diastereoisomer. After quaternization (MeI) and hydrolysis (2M HCl, pentane), (**3**) with $[\alpha]_D +91^\circ$ (*c* 1.1, MeOH)⁴ was obtained. The ^1H n.m.r. spectrum, measured in the presence of tris[(3-trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III), showed no methyl doublet corresponding to the enantiomer, confirming the optical purity of (**3**). Treatment of (**3**) with methyl-lithium followed by oxidation with pyridinium chlorochromate (PCC) afforded (**4**), $[\alpha]_D +95^\circ$ (*c* 1.3, CHCl_3); lit.⁵ $[\alpha]_D +93^\circ$ (CHCl_3). (*R*)-3,4-Dimethyl-2-cyclohexenone (**4**), thus in hand, was converted according to the reported procedure² to yield the (10*R*)-octalone intermediate (**1a**), $[\alpha]_D +16^\circ$ (*c* 1.1, MeOH).

Starting with (*R*)-(**1a**), we synthesised (–)-methyl kolavenate, which was chemically correlated to a number of neo-clerodane diterpenes, both *trans* and *cis*.⁶ After preliminary



Scheme 2. Reagents: i, Et_2AlCl , benzene-toluene; ii, L-Selectride, THF; iii, $\text{Me}_2\text{CHCMe}_2\text{BH}_2$, THF, then H_2O_2 , NaOH; iv, Bu^tCOCl , pyridine, then POCl_3 ; v, Bu^i_2AlH , PhMe; vi, AcOH, H_2O ; vii, NH_2NH_2 , KOH, $\text{HOCH}_2\text{CH}_2\text{OH}$; viii, MeSO_2Cl , Et_3N , CH_2Cl_2 ; ix, LiBr, THF; x, $\text{LiC}\equiv\text{CH}\cdot\text{EDA}$, Me_2SO ; xi, $\text{ZrCl}_2(\eta\text{-C}_5\text{H}_5)_2$, Me_3Al , then ClCO_2Me .

investigations on the racemic material to find a more efficient synthetic path from (1a) to (9), we performed the synthesis as in Scheme 2. Hydrocyanation of (1a) followed by reduction with L-Selectride gave the 3 α -alcohol (5), [α]_D +8° (c 1.1, MeOH) in 83% yield, which was hydroborated by triethylborane (Me₂CHCMe₂BH₂) and oxidized. After selective protection of the primary hydroxy group in the diol obtained, the secondary OH was eliminated to produce (6), [α]_D -126° (c 1.25, MeOH). The angular cyano group in (6) was transformed *via* an aldehyde to a methyl group and subsequent modification of the side chain functionality gave the bromide (7), [α]_D -41° (c 0.35, MeOH). The addition of the extra four skeletal carbon units in (9) was carried out in two steps.† Firstly, treatment of (7) with lithium acetylide-ethylene-diamine (EDA) complex gave the acetylenic compound (8), [α]_D -46° (c 0.35, MeOH) in 71% yield with unavoidable formation of the elimination product (<25%). The final conversion was effected by the application of Negishi's zirconium-catalysed carboalumination method.⁷ The metallation of (8) followed by treatment with methyl chloroformate furnished stereospecifically (-)-methyl kolavenate (9), [α]_D -58° (c 0.28, MeOH), [lit.⁸ -60.8° (c 2.07, EtOH)] in 31% yield (49% in the case of racemic material),‡ accompanied by variable amounts of the hydromethylated product. Our synthetic product (9) was indistinguishable from an authentic sample by comparison of spectral data (i.r. and ¹H n.m.r.) and t.l.c. behaviour.

Starting from (*R*)-amino-2-(methoxymethyl)pyrrolidine (RAMP)-hydrazone corresponding to (2), the method des-

cribed above can be used for the preparation of the (10*S*)-octalone intermediate, which will be useful for the chiral synthesis of *ent*-neo-clerodane diterpenes. This fact as well as the availability of (3)⁴ or (4)⁵ also from natural chiral sources will make our method of asymmetric synthesis widely applicable.

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† This conversion could also be achieved by the sequence: i, MeC≡CCH₂OMe, BuⁿLi; ii, (CO₂H)₂; iii, MnO₂, NaCN, AcOH, MeOH; but was less efficient.

‡ Hydrolysis of (9) to kolavenic acid was achieved by treatment with lithium hydroxide in aq. 1,2-dimethoxyethane at room temperature.