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

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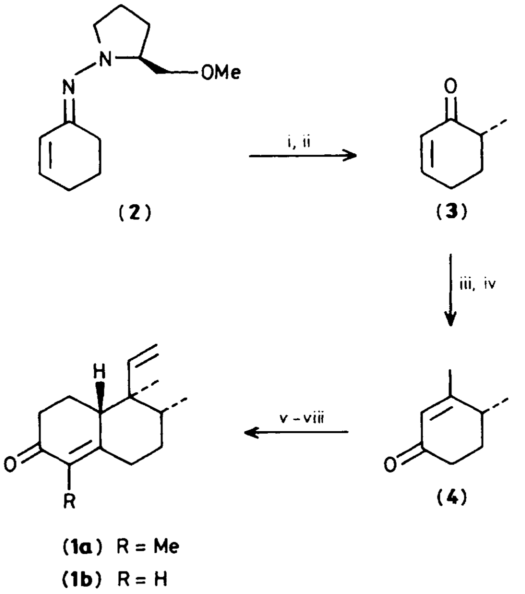
The asymmetric synthesis of (8*R*,9*S*,10*R*)-4,8,9-trimethyl-9-vinyl-Δ^4-3-octalone, a versatile intermediate for the syntheses of both *trans*- and *cis*-neo-clerodane diterpenoids, has been achieved by extension of Ender's asymmetric alkylation, and its utility is exemplified by the total synthesis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

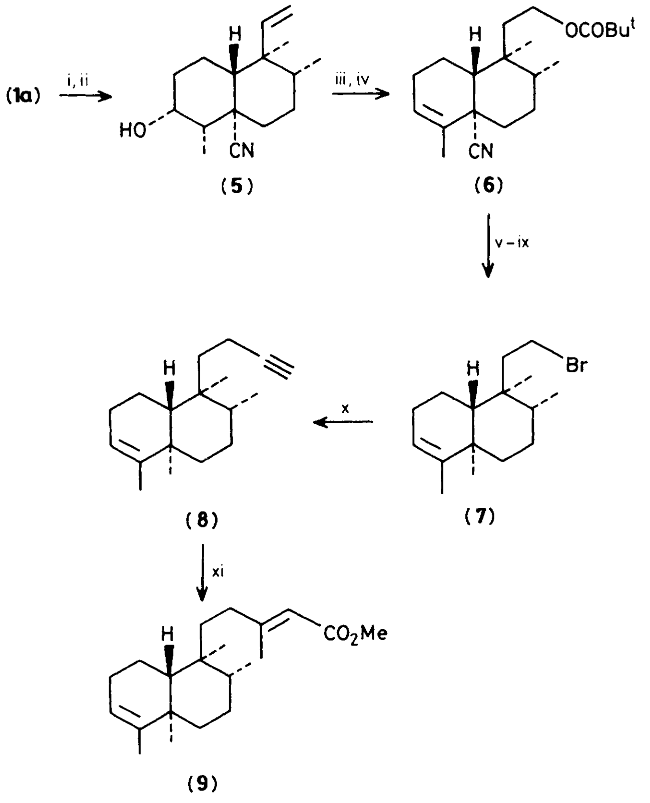
The problem of the absolute configuration in clerodane diterpenoids was settled only recently by the reappraisal of physical methods,[1] while a chiral synthesis of a clerodane diterpenoid, which should corroborate the conclusion, has not been reported. We report here a method for the asymmetric synthesis 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 methylated product, which exhibits a ^{1}H n.m.r. methyl signal only at δ 1.06 corresponding to one diastereoisomer. After quaternization (MeI) and hydrolysis (2 M HCl, pentane), (**3**) with $[\alpha]_D$ +91° (*c* 1.1, MeOH)[4] was obtained. The ^{1}H 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° (*c* 1.3, $CHCl_3$); lit.[5] $[\alpha]_D$ + 93° ($CHCl_3$). (*R*)-3,4-Dimethyl-2-cyclohexenone (**4**), thus in hand, was converted according to the reported procedure[2] to yield the (10*R*)-octalone intermediate (**1a**), $[\alpha]_D$ +16° (*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 1. *Reagents:* i, Pr^i_2NLi, THF, then *p*-$MeC_6H_4SO_3Me$; ii, MeI, then 2 M HCl, pentane; iii, MeLi, Et_2O; iv, PCC, CH_2Cl_2; v, CH_2=CHMgBr·$(Bu^n_3PCuI)_4$, THF, then CH_2O; vi, $MeSO_2Cl$, Et_3N, CH_2Cl_2; vii, $EtCOCH_2CO_2Me$, NaOMe, benzene; viii, 2 M HCl, MeOH, reflux.



Scheme 2. *Reagents:* i, Et_2AlCN, benzene–toluene; ii, L-Selectride, THF; iii, $Me_2CHCMe_2BH_2$, 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, $HOCH_2CH_2OH$; viii, $MeSO_2Cl$, Et_3N, CH_2Cl_2; ix, LiBr, THF; x, LiC≡CH·EDA, Me_2SO; xi, $ZrCl_2(\eta$-$C_5H_5)_2$, 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 3α-alcohol (**5**), $[\alpha]_D$ +8° (*c* 1.1, MeOH) in 83% yield, which was hydroborated by thexylborane ($Me_2CHCMe_2BH_2$) and oxidized. After selective protection of the primary hydroxy group in the diol obtained, the secondary OH was eliminated to produce (**6**), $[\alpha]_D$ −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**), $[\alpha]_D$ −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**), $[\alpha]_D$ −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**), $[\alpha]_D$ −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 described 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, $MeC{\equiv}CCH_2OMe$, Bu^nLi; ii, $(CO_2H)_2$; iii, MnO_2, 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.

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