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An improved general synthetic approach to *cis*-clerodane diterpenoids. A more efficient total synthesis of (±)-6β-acetoxy-2-oxokolavenool

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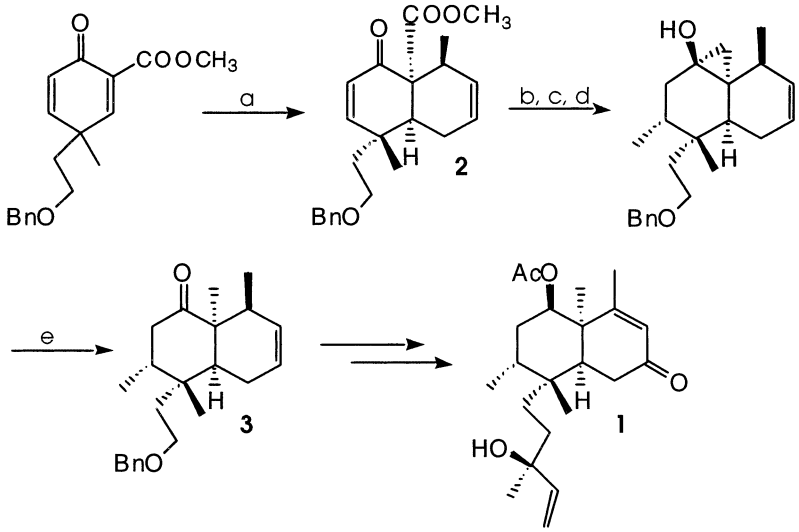
Abstract—The previously developed general synthetic approach to *cis*-clerodane diterpenoids has been greatly improved using 4-(2-benzyloxy)ethyl-2-cyano-4-methyl-2,5-cyclohexadien-1-one (**4**) as the starting dienophile. This approach allows the direct incorporation of an angular methyl group via reductive alkylation of the α-cyano ketone system. The viability of this approach to *cis*-clerodanes has been demonstrated in the alternative total synthesis of (±)-6β-acetoxy-2-oxokolavenool (**1**).

Clerodane diterpenoids are distributed widely in nature. More than eight hundred compounds have been isolated to date and many possess interesting biological activities.[1,2] Clerodanes are further subdivided more or less equally into the *trans*- and *cis*-series according to the stereochemistry about the ring junction of the decalin core. In view of the abundance of these structurally closely related natural products, a general synthetic scheme which allows easy access to many target molecules is desirable.[3] Such a scheme towards the *cis*-series has been developed in our laboratories recently, making use of a face-selective Diels–Alder reaction as the key operation[4–6] as illustrated in Scheme 1 with (±)-6β-acetoxy-2-oxokolavenool (**1**)[6] as a specific



Scheme 1. *Reagents and conditions*: (a) *trans*-piperylene, $ZnCl_2$, ether, 0°C, 68 h, 85%; (b) $(CH_3)_2CuLi$, ether, 0°C, 1 h; then $LiAlH_4$, 0°C, 0.5 h, 62%; (c) MsCl, Et_3N, THF, rt, 21 h; (d) NaI, Zn, DMF, 130°C, 28 h, 54% over two steps; (e) *p*-TsOH, CH_2Cl_2, rt, 40 min, 97%.

Keywords: reductive alkylation; α-cyano ketones; total synthesis.

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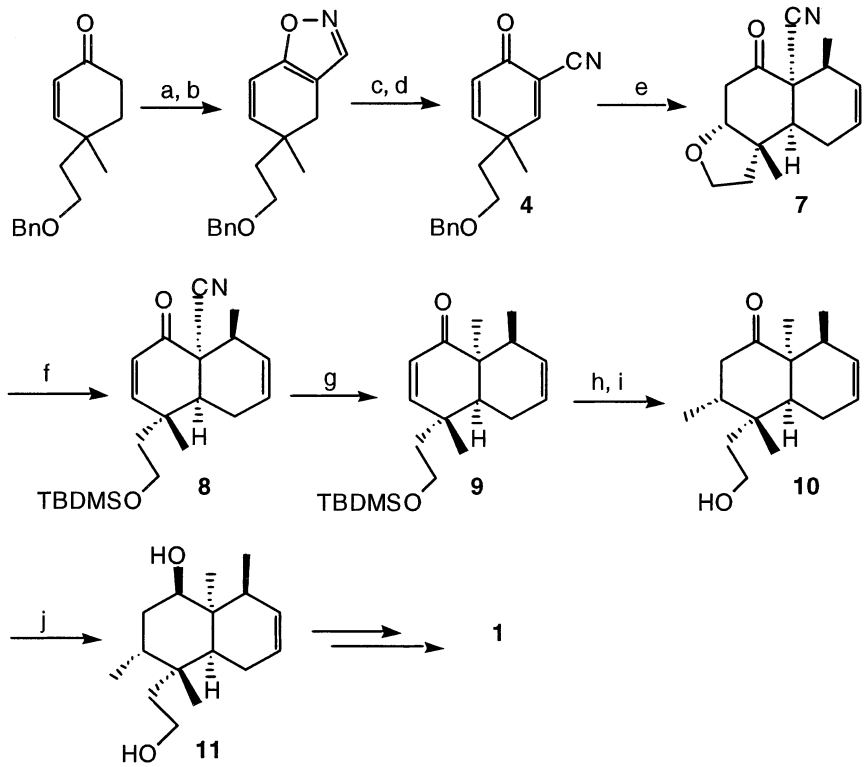
example. The generality of the scheme is apparent as it has been applied successfully to the total synthesis of several *cis*-clerodane diterpenoids.[5–7] However, the efficiency of the synthetic approach suffers somewhat from the lengthy operation (four steps, 30% overall yield) required for the conversion of the ester group to the angular methyl group (**2**→**3**). An improved synthetic approach has now been developed using cyano dienone **4** as the starting dienophile. This approach allows the direct installation of the required angular methyl group via a reductive alkylation process,[8] whereby the efficiency of the general synthetic approach to *cis*-clerodane diterpenoids is greatly enhanced.

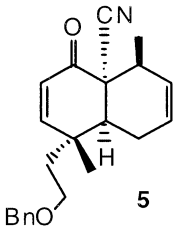
Cyano dienone **4** was readily prepared according to the sequence outlined in Scheme 2. 4-(2-Benzyloxy)ethyl-4-methyl-2-cyclohexenone[4] was formylated and the product converted to the corresponding isoxazole. Base induced rearrangement of the isoxazole ring followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ)[9] gave cyano dienone **4**.[10] Under Lewis acid catalysis, compound **4** was shown to undergo face-selective Diels–Alder reaction with *trans*-piperylene. Several Lewis acids were effective including $AlCl_3$, $CeCl_3$, $MgBr_2$, $ZnCl_2$ and $SnCl_4$. In each case, the preferential formation of the desired adduct **5** along with its stereoisomer **6** (ca. 3–5:1 ratio, 85–95% yield) was observed. More interestingly, when boron trichloride was applied as the Lewis acid, the cycloaddition occurred extremely rapidly (ca. 5 min at −78°C in methylene chloride) with concomitant cleavage of the benzyl ether group, giving rise, after aqueous work-up, to cyclic ether **7**[11] as the only product in 86% yield. Treatment of Diels–Alder adduct **7** with 1,5-diazabicyclo[5.4.0]undec-7-ene (DBU) and *t*-butyldimethylsilyl chloride (TBDMSCl) in refluxing tetrahydrofuran effected the opening of the ether ring to regenerate the conjugated enone moiety. The product **8** thus obtained was then subjected to reductive removal of the cyano group with lithium naphthalenide in tetrahydrofuran at −25°C. Trapping of the ensuing enolate with methyl iodide[8] proceeded with complete stereoselectivity giving directly the desired enone **9**[12] in 76% yield. This method of installing an angular methyl group represents a considerable improvement over the multistep process used in our original synthesis (vide supra) involving an ester group. Enone **9** was subjected to conjugate addition with lithium dimethylcuprate in ether in the presence of trimethylsilyl bromide[13] as an activating agent, and the product thus obtained was treated with tetra-*n*-butylammonium fluoride in tetrahydrofuran to give keto alcohol **10**. Lithium aluminum hydride reduction of **10** gave rise to diol **11**, an advanced intermediate in our previous synthesis of (±)-6β-acetoxy-2-oxokolavenool (**1**).[6] The sequence outlined in Scheme 2 constitutes a more efficient total synthesis, in racemic form, of the naturally occurring clerodane **1**.

The combination of Diels–Alder chemistry of the 2-cyano-2-cyclohexenone system and subsequent reductive methylation of the resulting cycloadduct provides a



Scheme 2. *Reagents and conditions*: (a) NaH, ethyl formate, EtOH (cat.), THF, rt, 4 h; (b) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH, reflux, 2 h, 73% over two steps; (c) NaOEt, EtOH, reflux, 2 h; (d) DDQ, THF, 1 h, 64% over two steps; (e) *trans*-piperylene, BCl_3, CH_2Cl_2, −78°C, 5 min, 86%; (f) DBU, TBDMSCl, THF, reflux, 8 h, 88%; (g) lithium naphthalenide, THF, −25°C; then CH_3I, rt, 24 h, 76%; (h) $(CH_3)_2CuLi$, TMSBr, −10°C, Et_2O, 24 h; (i) n-$Bu_4N^+F^-$, THF, rt, 2 h, 86% over two steps; (j) $LiAlH_4$, THF, 0°C, 30 min, 90%.

highly efficient access to the *cis*-decalin core found in *cis*-clerodane diterpenoids. The improved synthetic approach described above, in light of its efficiency and flexibility, represents a general solution to meet the synthetic challenge presented by the vast number of structurally closely related diterpenoids of the clerodane family.



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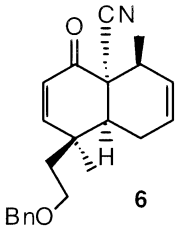

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10. Satisfactory spectral and elemental or HRMS analytical data were obtained for all new compounds. Where necessary, the stereochemistry was further confirmed by NOE experiments.
11. Compound **7**: IR (cast, $CHCl_3$): 1733 (ketone), 2224 cm^{-1} (CN); ^1H NMR (300 MHz, $CDCl_3$): δ 5.55 (t, $J=2$ Hz, 2H), 4.16 (td, $J=6$, 3 Hz, 1H), 3.88 (m, 2H), 3.03 (m, 1H), 2.96 (dd, $J=16$, 6 Hz, 1H), 2.66 (m, 1H), 2.64 (dd, $J=16$, 6 Hz, 1H), 2.57 (dd, $J=10$, 7 Hz, 1H), 2.48 (dm, $J=16$ Hz, 1H), 1.87–1.81 (m, 2H), 1.41 (d, $J=6$ Hz, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.2, 128.9, 123.6, 120.3, 83.4, 65.7, 49.7, 44.8, 42.5, 39.8, 38.5, 26.4, 25.4, 16.7; HRMS M^+: 345.1415. (calcd. for $C_{15}H_{19}NO_2$: 345.1415). Anal. calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71%. Found: C, 73.28; H, 7.70; N, 5.89%. The structure of this compound was further confirmed by a single crystal X-ray crystallographic analysis. The ether ring formation most likely occurred during the work-up and the chromatographic purification as the crude product consisted mainly of the alcohol precursor.
12. Compound **9**: IR (cast, $CHCl_3$): 1672 (ketone), 1090 (SiO), 710 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 6.56 (d, $J=10$ Hz, 1H), 5.95 (d, $J=10$ Hz, 1H), 5.64–5.71 (m, 1H), 5.49–5.52 (m, 1H), 3.56–3.60 (m, 2H), 2.18 (dm, $J=18$ Hz, 1H), 2.08 (m, 2H), 2.03 (d, $J=8$ Hz, 1H), 1.71–1.77 (m, 1H), 1.55–1.61 (m, 1H), 1.30 (s, 3H), 1.04 (s, 3H), 0.94 (d, $J=8$ Hz, 3H), 0.85 (s, 9H), −0.006 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 156.4, 130.5, 127.8, 123.9, 59.5, 45.7, 45.3, 40.5, 38.4, 36.8, 26.9, 25.8, 22.9, 22.4, 18.1, 17.6, −5.4; HRMS M^+: 348.2483 (calcd. for $C_{21}H_{36}O_2Si$: 348.2484).
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