An Efficacious Synthetic Strategy for *cis*-Clerodane Diterpenoids. Application to the Total Synthesis of (±)-6β-Acetoxy-2-oxokolavenool

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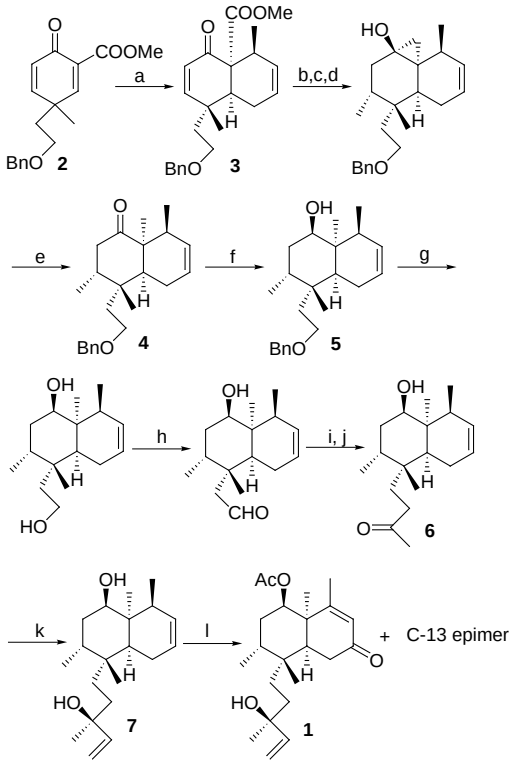
Abstract: An efficient synthetic strategy for *cis*-clerodane diterpenoids has been developed. The key ingredient is the face selective Diels–Alder reaction of dienophile **8**. The successful application of this strategy has culminated in the total synthesis of the naturally occurring compound 6β-acetoxy-2-oxokolavenool in racemic form.

Key words: reductive alkylation, α-cyano ketones, total synthesis, *cis*-clerodanes

Clerodane diterpenoids form a very large family of secondary metabolites; over one thousand members have so far been identified.[1] From a biological point of view, clerodanoids are rather interesting. A broad spectrum of significant biological activities has been found for the major portion of the relative few compounds screened.[2] According to the stereochemistry around the ring junction of the decalin nucleus, clerodanes are subdivided into the *trans*- and *cis*-series in roughly 2:1 ratio. During the past twenty years, extensive efforts have been devoted towards the total synthesis of this family of the diterpenoids.[3] Most of the synthetic approaches, however, are designed to tackle a specific target molecule. The natural abundance of a series of structurally closely related clerodanes dictates the development of a common strategy for their synthesis. Recently, a general approach to the *cis*-series of compounds has been developed in our laboratories.[4] As demonstrated in Scheme 1 with (+/–)-6β-acetoxy-2-oxokolavenool (**1**) as a specific example,[4c] the key operation involves the face selective Diels–Alder addition of dienone ester **2** to *trans*-piperylene allowing the rapid construction, in a highly stereoselective manner, of the required decalin core with concomitant placement of several functional groups into the strategic positions. This approach proved to be highly versatile. Its application has resulted in the successful synthesis of several other *cis*-clerodanes.[4b,c,5] However, there are a couple of drawbacks which reduce the overall efficiency of the synthetic approach. Both the installation of the angular methyl group (**3**→**4**) and the modification of the benzyl side chain to the butanone moiety (**5**→**6**) require lengthy operations (four steps each). We have since developed a considerably more efficient general strategy in which these problems have been successfully addressed. In this communication we wish to illustrate this newly developed synthetic strategy for *cis*-clerodanes using compound **1** as a specific example.



Scheme 1 Reagents and conditions: (a) *trans*-piperylene, $ZnCl_2$; (b) $(CH_3)_2CuLi$, then $LiAlH_4$; (c) MsCl, Et_3N; (d) NaI, Zn; (e) *p*-TsOH; (f) $LiAlH_4$; (g) Lithium naphthalenide; (h) $(Ph_3P)_3RuCl_2$; (i) α-methoxyethyltriphenyl phosphonium chloride, *n*-butyllithium; (j) 20% $HClO_4$; (k) vinylmagnesium bromide; (l) Ac_2O, DMAP, O_2, pyridine, TPP, hν, CCl_4.

The key to the success of the new synthetic strategy is the selection of compound **8** as the starting dienophile in which the cyano group could be readily transformed to a methyl group by a reductive alkylation process[6] and the 3-butenyl side chain to a 3-butanone moiety via the Wacker reaction;[7] each requires only a single operation. Compound **8**[8] was readily prepared (Scheme 2) by Stork–Danheiser alkylation[4c,9] of 6-methyl-3-ethoxy-2-cyclohexenone with 4-bromo-1-butene followed by $LiAlH_4$ reduction and treatment with hydrochloric acid. The cyano

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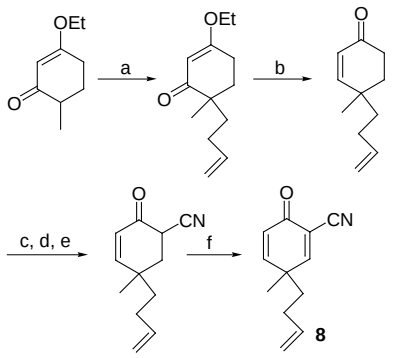
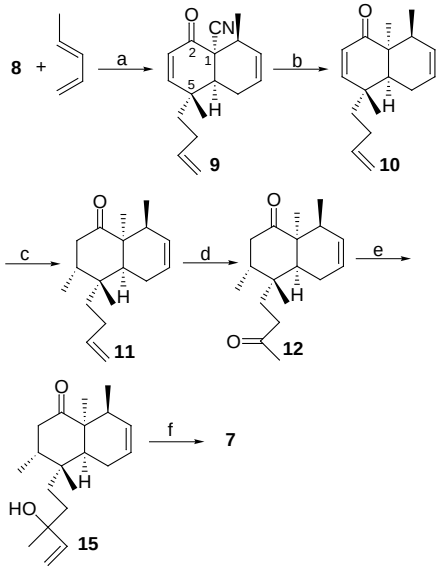
group was subsequently introduced via formylation, isoxazole formation and its rearrangement.[10] This was followed by DDQ oxidation[10a] to install the dienophilic double bond.

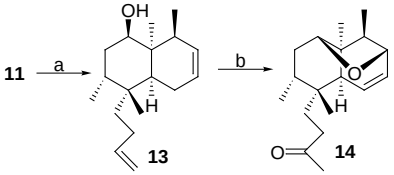


Scheme 2 Reagents and conditions: (a) LDA, THF, –78 °C, 1 h, then $BrCH_2CH_2CH{=}CH_2$, r.t., 60 h, 73%; (b) $LiAlH_4$ THF, r.t., 6 h, then 2 N HCl, r.t., 18 h, 95%; (c) NaH, HCOOEt, THF, r.t., 1 h, 73%; (d) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH, reflux, 2 h, 85%; (e) Na, EtOH, r.t., 2 h, 85%; (f) DDQ, K_2CO_3, THF, r.t., 3 h, 85%.

Under zinc iodide catalysis (Scheme 3), the Diels–Alder reaction of compound **8** and *trans*-piperylene occurred, as expected, mainly from the sterically less hindered face (methyl face) of the dienophile to give the desired adduct **9**[11] as the major product (73% yield). A small amount (12% yield) of its C-5 epimer was also produced as a result of the addition from the sterically more hindered face occupied by the butenyl side-chain. After serving as an activating as well as a directing group for the Diels–Alder reaction, the cyano group was readily replaced by a methyl group. Reductive alkylation of **9** by sequential treatment with lithium naphthalenide[12] and methyl iodide[6] gave an 83% yield of ketone **10**. This compound was then subjected to conjugate addition with lithium dimethylcuprate in the presence of trimethylsilyl bromide as an activating agent.[13] Upon treatment under the standard Wacker reaction conditions ($PdCl_2$, CuCl and O_2), [14] the addition product **11**, thus obtained in 85% yield, was readily oxidized to give the desired diketone **12**.[15] Interestingly, when alcohol **13** obtained from $LiAlH_4$ reduction of **11** was subjected to Wacker oxidation (Scheme 4), keto ether **14** was produced in 67% yield, apparently as a result of $PdCl_2$ catalyzed cyclization.[16] Diketone **12** was readily converted to (+/–)-6β-acetoxy-2-oxokolavenool (**1**) as follows. Selective Grignard addition of vinylmagnesium bromide to the sterically less hindered carbonyl group gave an inseparable mixture of epimeric ketols **15** (90% yield; 1:1) which was reduced with $LiAlH_4$ to give, in virtually quantitative yield, the known diols **7**.[4c] These epimeric diols were converted previously to the naturally occurring clerodane **1** and its C-13 epimer using a photooxygenation reaction.[4c,17]



Scheme 3 Reagents and conditions: (a) ZnI_2, Et_2O, r.t., 48 h, 73%; (b) Lithium naphthalenide, THF, –25 °C, 2 h, then CH_3I, r.t., 24 h, 83%; (c) $(CH_3)_2CuLi$, TMSBr, Et_2O, –10 °C, 3 h, 85%; (d) CuCl, $PdCl_2$, O_2, DMF–H_2O, r.t., 1.5 h, 85%; (e) $CH_2{=}CHMgBr$, THF, 0 °C, 2 h, 90%; (f) $LiAlH_4$, THF, 0 °C, 98%.



Scheme 4 Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 1 h, 85%; (b) CuCl, $PdCl_2$, O_2, DMF–H_2O, r.t., 3 h, 67%.

The foregoing discussion shows that a rather complex clerodane diterpenoid (i.e. **1**) can be prepared from a readily accessible dienophile (i.e. **8**) in seven steps and 12% overall yield. This highly effective synthetic strategy, with appropriate minor adjustments, should also facilitate the total synthesis of many natural products of the *cis*-clerodane family, which is currently under active investigation.

Acknowledgement

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References and Notes

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(11) Compound **9**: IR (neat, cm^{-1}): 2230 (CN), 1702 (C=O), 1640, 1616 (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ = 6.47 (dd, *J* = 10, 1.5 Hz, 1 H, C**H**=CHCO), 5.92 (d, *J* = 10 Hz, 1 H, CH=C**H**CO), 5.76–5.85 (m, 1 H, CH_2=C**H**), 5.56 (br. s, 2 H, C**H**=C**H**), 5.05 (dd, *J* = 17, 1.5 Hz, 1 H, *trans* CH=C**H**H), 4.98 (dd, *J* = 10, 1.5 Hz, 1 H, *cis* CH=CH**H**), 2.69–2.73 (m, 1 H), 2.56–2.61 (m, 1 H), 2.12–2.24 (m, 4 H), 1.82–2.00 (m, 2 H), 1.38 (d, *J* = 7.5 Hz, 3 H, CHC**H**$_3$), 1.09 (s, 3 H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.84 (C=O), 155.20 (CH), 137.60 (CH), 128.79 (CH), 125.28 (CH), 123.73 (CH), 120.91 (C), 115.27 (CH_2), 48.40 (C), 42.06 (CH), 40.11 (C), 38.98 (CH_2), 37.71 (CH), 28.64 (CH_2), 25.02 (CH), 24.04 (CH_3), 16.85 (CH_3); HRMS: M^+ = 255.1617 (calcd for $C_{17}H_{21}ON$: 255.1623).
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(15) Compound **12**: IR (neat, cm^{-1}): 1712 (C=O), 1694 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.78–5.84 (m, 1 H, C**H**=CH), 5.66–5.71 (m, 1 H, CH=C**H**), 2.35–2.41 (m, 2 H), 2.01–2.34 (m, 6 H), 2.15 (s, 3 H, COC**H**$_3$), 1.84 (td, *J* = 7, 1 Hz, 1 H, C**H**CH_3), 1.48–1.55 (m, 2 H), 1.19 (s, 3 H, C**H**$_3$), 0.95 (d, *J* = 6 Hz, 3 H, C**H**$_3$), 0.86 (s, 3 H, C**H**$_3$), 0.85 (d, *J* = 6 Hz, 3 H, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.68 (C=O), 208.48 (C=O), 132.49 (CH), 126.41 (CH), 50.83 (C), 46.89 (CH), 44.99 (C), 39.27 (CH), 38.42 (CH_2), 37.55 (C), 35.79 (CH), 30.05 (CH_3), 29.33 (CH_3), 29.25 (CH_2), 23.46 (CH_2), 22.73 (CH_3), 17.10 (CH_3), 15.88 (CH_3); HRMS: M^+ calcd for $C_{18}H_{28}O_2$: 276.2089; found, 276.2089
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