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IRIDOIDS : STEREOSPECIFIC SYNTHESIS OF FUNCTIONALIZED CYCLOPENTANOID INTERMEDIATES VIA BICYCLO|2.2.1|HEPTANONES

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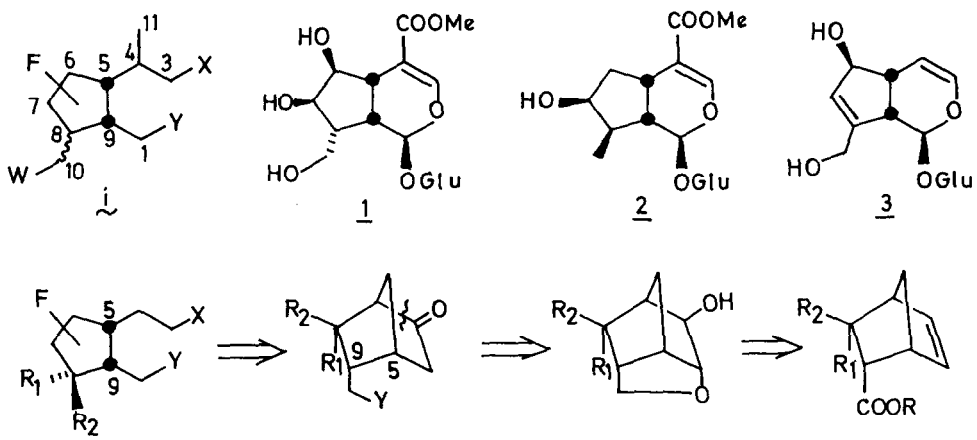
ABSTRACT

An efficient synthesis of functionalized trialkyl substituted cyclopentanoids is presented. Stereocontrol is secured by their formation from norbornane precursors. The strategy is illustrated by the total synthesis of (±)-boschnialactone (13), (±)-teucriumlactone C (14) and (±)-loganin (2).

The iridoids[3], with ca 300 known naturally occurring compounds, represent a class of highly oxygenated monoterpenoids, characterized by a functionalized (F) cyclopentane ring cis-fused to a dihydropyran (e.g. 1, 2 and 3), δ-lactone (e.g. 13 and 14) or δ-lactol ring. Next to the normal monoterpenes (10 carbon atoms), a number of iridoids are found having a 9-carbon skeleton which lack C-11 as in aucubin (3) or exceptionally C-10. The configuration at C-8 (when not sp^2 hybridized) can be α as in nycthantoside (1) or β as in loganin (2).



1 2 3

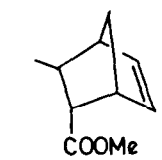
i

ii $R_1 = H$; R_2 = 1 - C(W)
iii R_1 = 1-C(W) ; $R_2 = H$

Scheme 1

The 10-position is frequently oxygenated (e.g. 1 and 3). Established strategies for iridoid synthesis involve oxidative cleavage of cis-bicyclo|3.3.0|octenenes[4] or annulation of the heterocyclic ring using Büchi's variant[5] of the de Mayo reaction[6]. These approaches are mainly directed towards a subgroup or a single representative. High stereocontrol is observed because of the roof-top shape of the bicyclic intermediates.

We presently describe a novel strategy which allows for a general and efficient entry into the different subclasses via functionalized (F), trialkyl substituted five-membered rings ii and iii with differentiated oxygen-functionalities (X, Y, W in i, ii and iii) present in the 2C and 1C carbon units (scheme 1). As these intermediates are obtained via fragmentation (Norrish I type reaction or Baeyer-Villiger oxidation) of norbornane precursors complete stereospecificity is secured. These precursors are assembled by a Diels-Alder reaction of a suitable Z (→ iii) of E (→ ii) dienophilic olefin with cyclopentadiene followed by oxidative cyclization. Here we report the synthesis of some simple iridoids with W=H as illustrative examples of the new strategy[7].



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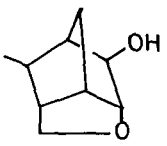

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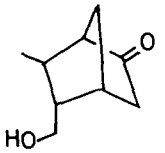

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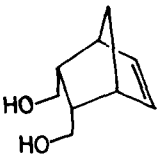

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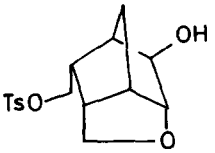

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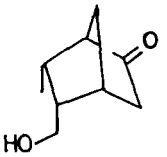

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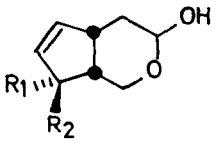
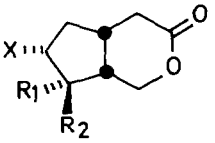


10 R_1 = H; R_2=Me

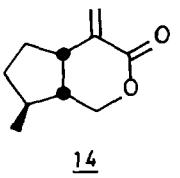
11 R_1 =Me; R_2=H



12 R_1 =H; R_2=Me; X=H

13 R_1 =Me; R_2=H; X=H

15 R_1 =H ; R_2=Me; X=OH



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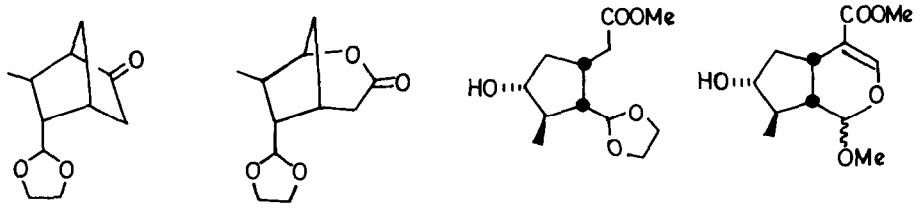
Scheme 2

The norbornene 4 (scheme 2), starting material for the C-8, β series ii (W=H), was obtained in 84 % yield from cyclopentadiene (2.5 eq) and methyl E-crotonate with Et_2AlCl (1.25 eq) as catalyst (CH_2Cl_2, 48 h, -78°C - 0°C). The endo-exo stereoselectivity was 15:1; after reduction with LAH, exclusively the endo-alco-

hol cyclized to 5 upon treatment with mCPBA in CH_2Cl_2[8] (2.5 h, 20°C) in 83 % overall yield. Swern oxidation[9] (87 %) followed by reductive cleavage of the ether bond (Al-Hg, THF, EtOH, 2 h, 93 %) afforded the desired norbornanone 6. The epimer 9 was obtained from the known endo-adduct of cyclopentadiene and maleic anhydride which upon LAH reduction afforded diol 7[10]. Treatment with mCPBA as described for the formation of 5, followed by selective tosylation gave 8 in 60 % overall yield. Reductive removal[11] of the tosylate (super-H, THF, 1 h reflux, 88 %) followed by Swern oxidation (80 %) and Al-Hg treatment (86 %) afforded 9. The conceptually shorter synthesis involving methyl Z-crotonate is not attractive because of its difficult accessibility[12] and low stability under the reaction conditions. Furthermore the present route is also suitable for C-10 functionalized iridoids (i and ii; W = oxygen function) such as 1 and 3 and allows an entry into chiral synthesis after resolution of a suitable mono-O-substituted derivative of the symmetrical diol 7.

With both 6 and 9 in hand we could now study the projected bond cleavage. Norrish I type reaction (254 nm in CH_3CN for 17 h) of 9 afforded 11 in > 90 % yield; oxidation[13] (PCC, CH_2Cl_2, 4 h) of the crude lactol and double bond hydrogenation (Pd-C, EtOH) gave (±)-boschnialactone[14,15] (13) in 75 % overall yield. The configuration of the C-8 epimers is evident from the reaction sequence. Isomer 12 (from 6 as described for 9-13) was transformed into (±)-teucriumlactone C[16] (14) using Grieco's method[17] for the introduction of the α-methylene group ((1) H_2CO, LDA; (2) MsCl; (3) DBU; 47 %).

The alternative cleavage of 6 involving a Baeyer-Villiger oxidation (mCPBA, CH_2Cl_2) and spontaneous translactonization of the initially formed lactone led to 15, an intermediate of interest for lactonic iridoids. For the synthesis of a dihydropyran ring system as present in loganin (2), the C-1 atom in 15 is not at the desired oxidation level. Therefore 6 was first transformed into 16 in 76 % yield by Swern oxidation and selective transacetalization with 2-methyl-2-ethyl dioxolane ((1) p.TsOH, CH_2Cl_2, 45 min, 20°C; (2) MeCOMe, p.TsOH, 4h, 20°C).



16 17 18 19

Scheme 3

Oxidation with mCPBA gave 17 (75 %) which resisted Claisen condensation with methyl formate[18]. After lactone ring opening (MeOH-NaOMe 0.5 eq, 24 h, 20°C; 97 %) and protection of the hydroxyl function (MEMCl, CH_2Cl_2, i.Pr_2EtN, 20°C) the formyl group could be introduced upon metallation with a 1:1 mixture of t.BuOK-LiICA at

-78° in HMPA-THF. Acid work-up and treatment with p.TsOH in MeOH for 48 h at room temperature gave 19 in 48 % yield from 18, as an epimeric mixture at C-1. As the mayor β isomer of 19 has been transformed by Büchi[5] into (±)-loganin (2), its formation represents a formal synthesis of 2.

Application of this strategy for the synthesis of highly functionalized iridoids as well as other cyclopentanoid natural products is presently being investigated.

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