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A new route to furanoeremophilane sesquiterpenoids. Synthesis of (±)-6β-hydroxyeuryopsin

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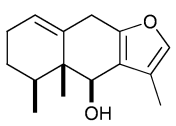
The naturally occurring furanoeremophilane 6β-hydroxyeuryopsin was synthesized by a novel route which involved Stille coupling of a 2-furylstannane with a cyclohexylmethyl bromide, followed by intramolecular formylation of the furan to complete the tricyclic nucleus of the sesquiterpenoid.

The eremophilane family is a large, structurally diverse group of sesquiterpenoids characterized by a decalin skeleton in which a methyl migration has taken place to produce a non-isoprenoid substituent pattern.[1] A subset of this group, the furanoeremophilanes, bears a furan fused to the decalin core which, in certain cases, appears in oxidized form as a butenolide.

Beginning in 1971 with Piers' pioneering synthesis of (±)-eremophilenolide,[2] a substantial synthetic effort has been devoted to this class of natural products with the result that several distinct pathways have been established.[3] However, none of these builds the furanoeremophilane framework through consecutive alkylations at C2 and then C3 of a preformed furan. We now describe a synthesis of 6β-hydroxyeuryopsin (**1**), a furanoeremophilane isolated from *Senecio tolucannus*,[4] which exemplifies just such a strategy, and which, in principle, allows access to a broad array of related sesquiterpenoids such as petasalbine (**2**) and ligularone (**3**).[5]



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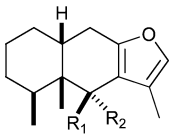
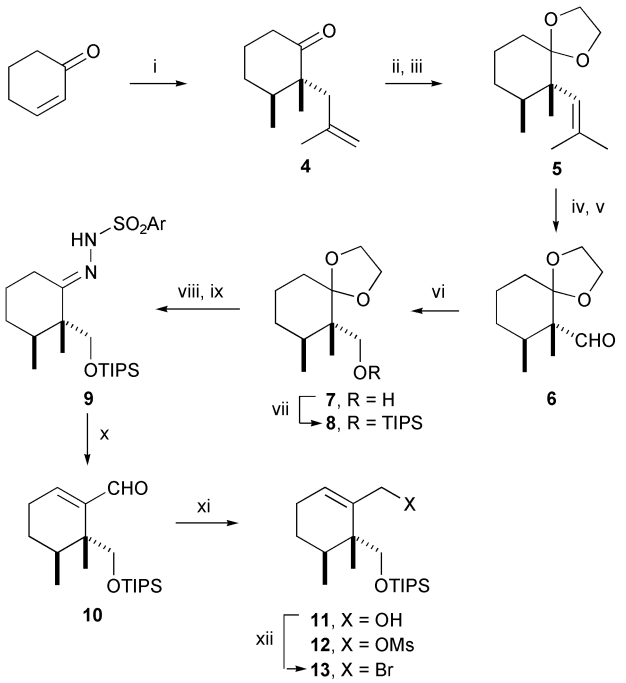


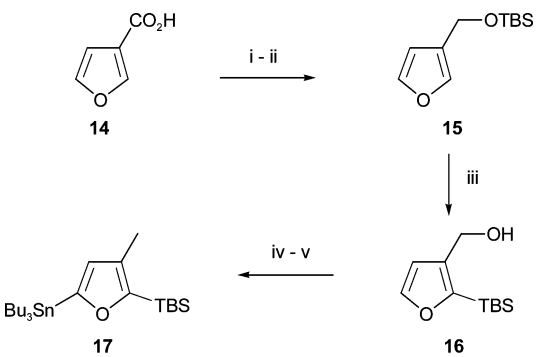
2, R_1 = OH, R_2 = H
3, R_1, R_2 = O

The synthesis of **1** commenced from the known 2,3-dimethyl-2-methallylcyclohexanone (**4**),[6] prepared as a 4 : 1 mixture of *cis* and *trans* isomers from 2,3-dimethylcyclohexanone (Scheme 1). Ketalization of the major isomer **4** was selective and was followed by acid-catalyzed isomerization of the terminal alkene to yield the trisubstituted olefin **5**. This was subjected to oxidative cleavage to give aldehyde **6**.[7] The latter was reduced, and the resulting primary alcohol **7** was protected as its triisopropylsilyl (TIPS) ether **8**. Mild acidic hydrolysis of ketal **8** under conditions that left the TIPS ether intact produced a ketone which was condensed with 2,4,6-triisopropylbenzenesulfonylhydrazine. Shapiro reaction[8] of hydrazide **9** with *tert*-butyllithium, followed by treatment of the intermediate lithio alkene with dimethylformamide, afforded α,β-unsaturated aldehyde **10** which was reduced to primary alcohol **11**. This compound was converted *via* its mesylate **12** to allylic bromide **13**.

The furanoid partner required for coupling with **13** was obtained from furan-3-carboxylic acid (**14**) (Scheme 2). After reduction of this acid with borane and conversion of the resulting primary alcohol to *tert*-butyldimethylsilyl (TBS) ether **15**, the furan was reacted with *n*-butyllithium in HMPA to yield **16**. This transformation is presumed to occur *via* an intramolecular retro-Brook rearrangement[9] of the corresponding 2-lithiofuran and conveniently blocks C-2 of the furan against further substitution at this position. After reductive cleavage of the mesylate of **16** with lithium triethylborohydride, lithiation of the furan with *n*-butylli-



Scheme 1 *Reagents and conditions*: i, Ref. 6; ii, 2-ethyl-2-methyl-1,3-dioxolane, $(CH_2OH)_2$, *p*-TsOH (0.2 equiv.), rt, 72 h, 75%; iii, *p*-TsOH (0.05 equiv.), benzene, 50 °C, 12 h, 57%; iv, K_2OsO_4 (0.05 equiv.), $K_2Fe(CN)_4$, K_2CO_3, quinolidine, $MeSO_2NH_2$, *t*-BuOH–H_2O, rt, 48 h, 90%; v, $NaIO_4$, THF, H_2O, rt, 12 h, 100%; vi, $NaBH_4$, THF–H_2O, rt, 12 h; vii, TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to 0 °C, 4 h, 93%; viii, PPTS (0.3 equiv.), 10% aq. acetone, 60 °C, 4 h, 85%; ix, 2,4,6-triisopropylbenzenesulfonylhydrazine, THF, rt, 12 h, 100%; x, *tert*-BuLi, 10% TMEDA–hexanes, −78 °C, 30 min, then 0 °C, 1 min, then −78 °C, DMF, −78 °C to 0 °C, 4 h; xi, DIBALH, CH_2Cl_2, −78 °C to 0 °C, 4 h, 75% from **9**; xii, Ms_2O, Et_3N, CH_2Cl_2, −78 °C to 0 °C, 2 h, then LiBr, THF, rt, 12 h, 95%.



Scheme 2 *Reagents and conditions*: i, BH_3·Me_2S, THF, rt, 12 h, 85%; ii, TBSCl, imidazole, CH_2Cl_2, rt, 2 h, 100%; iii, *n*-BuLi, HMPA–THF, −78 °C to rt, 6 h, 89%; iv, Ms_2O, Et_3N, CH_2Cl_2, −78 °C to 0 °C, 2 h, then $LiEt_3BH$, THF, 0 °C, 100%; v, *n*-BuLi, THF, −78 °C to 0 °C, 6 h, then *n*-Bu_3SnCl, −78 °C to rt, 12 h, 85%.

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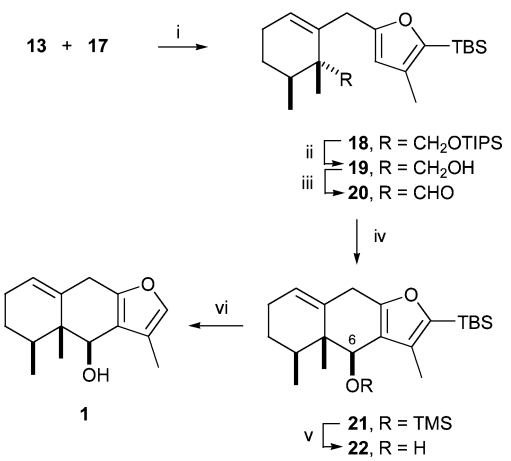
thium took place exclusively at C-5, and subsequent addition of tri-*n*-butyltin chloride[10] cleanly furnished the furyl stannane **17**.

Stille coupling[11] of allylic bromide **13** with stannane **17** was carried out in the presence of catalytic palladium(0) dibenzylideneacetone complex and triphenylarsine to furnish the alkylfuran **18** in good yield (Scheme 3). Removal of the TIPS ether and oxidation of the resulting primary alcohol **19** to aldehyde **20** set the stage for closure to the tricyclic eremophilane skeleton. After considerable experimentation with a variety of Lewis acids, it was found that cyclization of **20** could be accomplished in quantitative yield with trimethylsilyl triflate in the presence of 2,6-lutidine. The initial product was the trimethylsilyl (TMS) ether **21** accompanied by 15% of its 6α epimer. Selective cleavage of the TMS ether from this mixture produced alcohol **22** which formed a crystalline *p*-nitrobenzoate ester, and X-ray crystallographic analysis of this derivative fully confirmed the stereostructure of **22** (Fig. 1).† Removal of the TBS ether from the furan moiety of **22** required strenuous conditions but was accomplished with a 2 M solution of TBAF in THF[9] and gave a substance identical with the natural product 6β-hydroxyeuryopsin (**1**) based on comparison of NMR spectra.[4]

In summary, a new pathway to furanoeremophilanes has been established which constructs the tricyclic framework from a 2-alkylfuran through closure of the central cyclohexane ring. As exemplified in the synthesis of **1**, the route exhibits good control of relative stereochemistry and is characterized by a novel tactic for directing substitution at a reactive furan.

We are indebted to Professor Alexandre F. T. Yokochi of this Department for the X-ray crystal structure, and to Professor Romo de Vivar, Universidad Nacional Autónoma de México, for NMR spectra of natural 6β-hydroxyeuryopsin. Financial support was provided by the National Science Foundation (01076103-CHE).



Scheme 3 *Reagents and conditions*: i, $Pd_2(dba)_3$ (0.2 equiv.), $AsPh_3$ (0.8 equiv.), THF, rt, 48 h; ii, TBAF, THF, rt, 12 h, 85% from **13**; iii, TPAP (0.05 equiv.), 4 Å mol sieves, *N*-methylmorpholine-*N*-oxide, CH_2Cl_2, rt, 2 h, 85%; iv, TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 12 h, 100%; v, TBAF, THF, rt, 2 h; vi, 2 M TBAF (20 equiv.), THF, rt, 24 h, 60% from **21**.

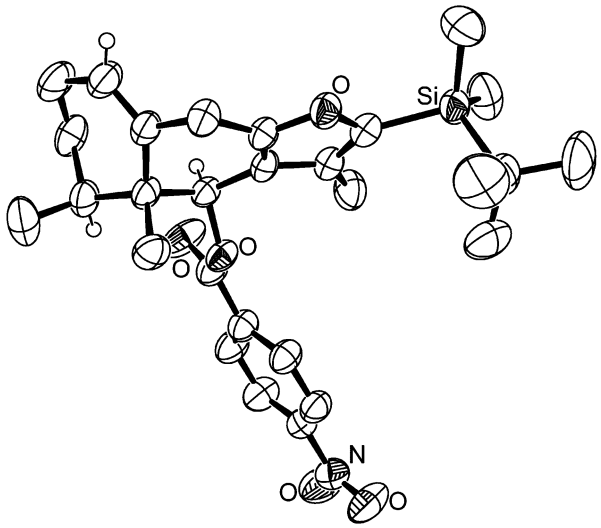


Fig. 1 ORTEP plot of the crystal structure of the *p*-nitrobenzoate of **22**. Thermal ellipsoids are drawn at the 30% probability level.

Notes and references

† *Crystal data for p-nitrobenzoate of **22***: M = 495.68; triclinic, space group $P\bar{1}$; a = 7.479(2), b = 8.389(3), c = 22.545(9) Å, β = 99.07(3)°, V = 1379.1 (8) A^3, T = 293(2) K; Z = 2; μ = (Cu-Kα) = 1.045 mm^{-1}; reflections: total = 5964, unique 4750 (R_{int} 0.0279); residuals (all data Shelxl): $R1$ = 0.0803, $wR2$ = 0.2000. CCDC 220193. See http://www.rsc.org/suppdata/cc/b3/b311211j/ for crystallographic data in .cif or other electronic format.

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