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Synthesis of the trinervitane ring system

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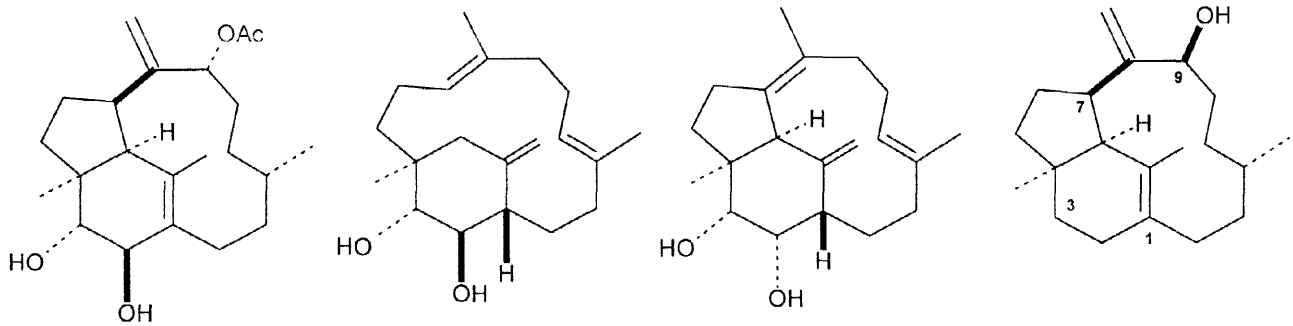
Dedicated to the memory of William G. Dauben

Abstract: The synthesis of the basic tricyclic nucleus of the trinervitane diterpenes by means of the *Robinson* annelation and *McMurry* coupling is described.

Keywords: indanes; terpenes and terpenoids

While other families of termites have physical defense mechanisms, the *nasute* termite subfamily is protected solely by chemical means. Thus, a glue like mixture of terpenoids is stored in the enlarged heads of the soldiers and delivered through their elongated nose on intruders. This mixture has been found to contain monoterpenes as well as cembrene derived diterpenes such as trinervi-2β, 3α, 9α-triol 9-O-acetate **1** [1] and secotrinervitene-2β, 3α-diol **2** [2].



1 **2** **3** **4**

The synthesis of racemic secotrinervitane **2,** has been accomplished [3]. To date, however, there has been only a single reported synthesis of the trinervitane skeleton. Thus, starting from **2,** Kato et al. used a novel transannular ring construction to prepare **3** with the correct trinervitane skeleton but improper positioning of the unsaturated functionality [4]. Our initial trinervitane target **4** [5] was later shown [6] to have the hydroxy group at C3 on the cyclohexyl ring and not at C9 as initially assigned. Herein, we wish to present our synthesis toward the putative **4** culminating in a new route to the unique tricyclic trinervitene skeleton with correct placement of the two double bond functionalities.

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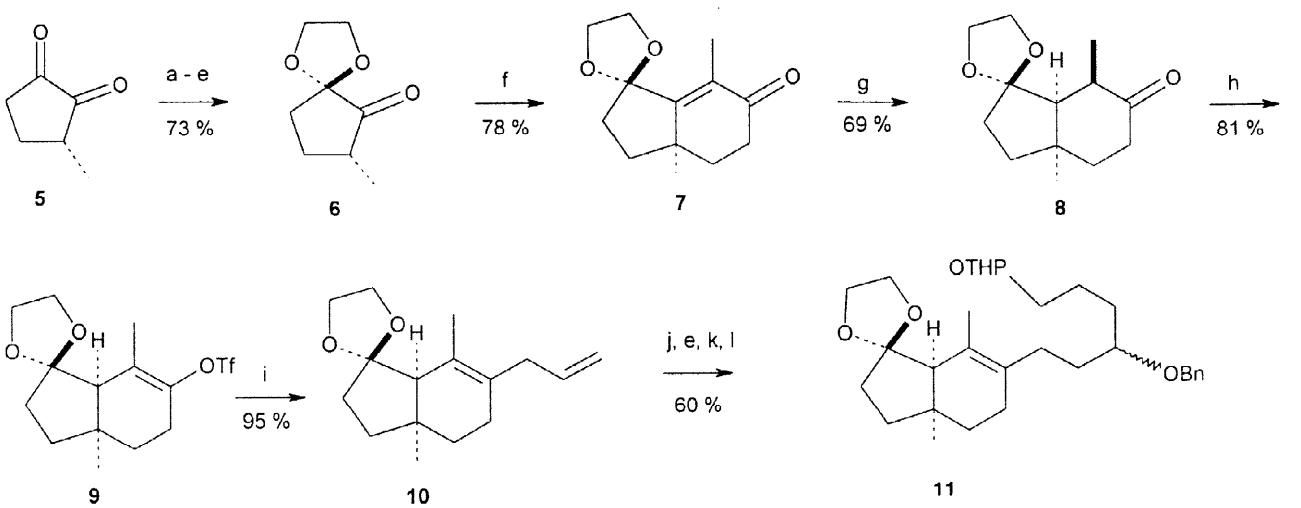
The basic strategy was to rapidly construct the requisite hydrindane carbon skeleton present in trinervitane allowing carbonyl functionality at C1 and C7 to provide access to the 11-membered carbocylic ring fused to these positions. A palladium mediated coupling reaction was envisaged to fix the tetrasubstitued olefin and introduce a carbon chain at C1 which would subsequently be closed on a chain emanating from C7. Starting material cyclotene **5** from the flavors and fragrances industry [7] was transformed into **6** (bp. 56°C 1.0mm, 73%)[3] in an efficient five step sequence on a hundred gram scale (**Scheme 1**). Robinson annulation of **6** with ethylvinyl ketone proceeded smoothly to give hydrindenone **7** also on a multi gram scale (bp. 135-140°C 0.75mm, mp. 58-59°C, 78%). Catalytic hydrogenation of **7** at ambient pressure was slow and performed in the presence of K_2CO_3 to prevent deketalization. The crude 9:1 mixture of *cis* and *trans* hydrindanones was recrystallized twice from hexane to give pure *cis*-hydrindanone **8** (mp. 102-5°C, 69%)[4]. The structure of **8,** a system for which there is surprisingly little precedent [8,9], was unequivocally assigned by single crystal *X*-ray analysis. The key regiospecific synthesis of enol triflate **9** was achieved via thermodynamic enolate formation in Et_2O/HMPA (5:1) by adding **8** to 0.95eq. of BrMgN(*i*-Pr)$_2$ at room temperature [10] and trapping with $PhNTf_2$ [11] after 1 day of equilibration (SiO_2 7% EtOAc-hexane, 81%). Stille coupling [12] of **9** with tri-n-butylallyltin afforded **10** in excellent yield (SiO_2 3% EtOAc-hexane, 95%).

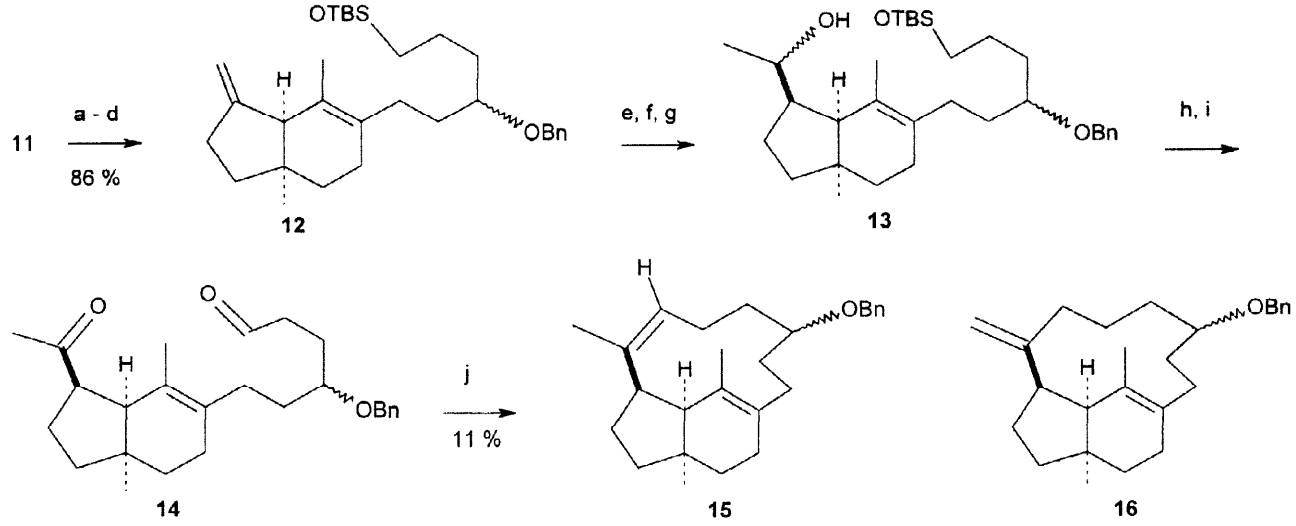


Scheme 1

Key: a) Ac_2O, reflux; b) H_2, 10%Pd/C, AcOEt; c) HO-$(CH_2)_2$-OH, TsOH, C_6H_6, reflux; d) NaOMe (cat.), MeOH; e) $(COCl)_2$-DMSO, CH_2Cl_2, Et_3N f) NaOMe, MeOH, ethylvinylketone, 0°C to reflux; g) H_2, 10%Pd/C, K_2CO_3, AcOEt; h) 0.95 eq. BrMgN(*i*-Pr)$_2$, Et_2O/HMPA, 24h then $PhNTf_2$ 16h; i) 5 eq. LiBr, Bu_3Sn-allyl, $Pd(Ph_3)_4$, THF reflux; j) 9-BBN, THF, 0°C to rt then 3N NaOH, 30% H_2O_2; k) Li-$(CH_2)_3$-OTHP, Et_2O, -60°C; l) NaH, THF, 1h then BnBr, Bu_4NI (cat.).

3) All new compounds listed in the manuscript gave satisfactory spectral and elemental (±0.4% C, H) or MS-analytical data.
4) ^{1}H-NMR (400MHz, $CDCl_3$): δ 3.76-3.93 (m, 4H), 2.45 (dq, 1H), 2.43 (ddd, 1H), 2.23 (ddd, 1H), 2.20 (d, 1H), 1.78 (ddd, 1H), 1.60-1.77 (m, 3H), 1.57 (ddd, 1H), 1.47 (bq, 1H), 1.23 (s, 3H), 1.07 (d, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 213.1, 118.5, 64.2, 63.5, 56.3, 40.6, 38.5, 35.8, 35.0, 34.1, 33.6, 29.2, 11.9.

With this two-step sequence the introduction of the side chain as well as the regiochemically correct setting of the tetrasubstituted double bond was achieved in an efficient manner. 9-BBN mediated hydroboration of the terminal double bond followed by oxidation [13] and condensation with Li-$(CH_2)_3$-OTHP[5] afforded, after benzylation, **11** as a ca. 1:1 mixture of diastereoisomers at the side chain center (SiO_2 15% EtOAc-hexane, 60%) [6].



Scheme 2

Key: a) $(CO_2H)_2/SiO_2$, CH_2Cl_2; b) CH_2Br_2/Zn, $TiCl_4$, THF, -30°C to rt; c) cat. TsOH, MeOH; d) TBDMSCl, Et_3N, cat. DMAP, CH_2Cl_2; e) 9-BBN, THF, 0°C to rt then 3N NaOH, 30% H_2O_2; f) $(COCl)_2$, DMSO, Et_3N, THF; g) MeLi; h) TBAF, THF; i) PCC/Al_2O_3, CH_2Cl_2; j) $TiCl_3(DME)_{1.5}$, Zn-Cu, DME, reflux.

Subsequent deketalization on acidified silica gel (**Scheme 2**) was accompanied by partial loss of the THP blocking group. Standard methylenation of the mixture under Wittig conditions could not be achieved but proceeded smoothly using the non-basic CH_2Br_2/Zn, $TiCl_4$ reagent [14]. The primary hydroxy group was fully deprotected and converted into *t*-butyldimethylsilyl ether **12** (SiO_2 3% EtOAc-hexane, 86%)[7]. 9-BBN mediated hydroboration of **12** occurred almost exclusively from the less hindered convex face. The primary alcohol was oxidized and the resulting aldehyde treated in situ with MeLi yielding **13** with the correct relative configuration at C9 (SiO_2 7-20% EtOAc-hexane, 48%) [15]. After deprotection the resulting diol was oxidized cleanly using an excess of PCC/Al_2O_3 to give ketoaldehyde **14** without loss of stereochemical integrity at C9 (SiO_2 20% EtOAc-hexane, 56%)[8]. With this compound in our hand we were ready to close the 11-membered ring via McMurry reaction.

5) Li-$(CH_2)_3$-OTHP was prepared through direct metallation of the corresponding bromide. Use of silyl protected bromopropanols led to cyclopropanes during metallation.

6) This stepwise introduction of the sidechain left us with a functionality in the correct position for the introduction of the methyl group found in the natural products.

7) ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.27-7.40 (m, 5H), 4.84 (m, 2H), 4.54 (m, 2H), 3.65 (m, 2H), 3.42 (m, 1H), 2.37 (m, 2H), 2.32 (bs, 1H), 1.99-2.19 (m, 4H), 1.79 (s, 3H), 1.41-1.70 (m, 10H), 1.21 (m, 1H), 0.98 (s, 3H), 0.93 (s, 9H), 0.08 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.94/155.95, 139.03, 129.89/129.91, 128.25, 127.66, 127.34, 125.29, 106.31, 78.76, 70.61, 63.22, 57.70, 39.71, 36.14/36.19, 32.13/32.15, 30.47/30.50, 29.86, 29.76, 28.98/29.02, 28.63/28.66, 27.20, 25.95, 25.36/25.42, 19.13/19.18, 18.32, -5.29. Calc. for $C_{31}H_{50}O_2Si$ C 77.12, H 10.44; found C 77.39, H 10.62.

8) Oxidation of the secondary hydroxyl followed by F^- mediated deprotection led to epimerization at C9. ^{1}H-NMR (400MHz, $CDCl_3$): δ 9.75 (t, 1H), 7.26-7.37 (m, 5H), 4.52 (d, 1H), 4.45 + 4.44 (d, 0.5H each), 3.41 (m, 1H), 3.31 (ddd, 1H), 2.53 (m, 2H), 2.17 (bd, 1H), 1.47-2.18 (m, 13H), 2.09 (s, 1.5H), 2.08 (s, 1.5H), 1.67 (s, 3H), 1.18 (m, 1H), 0.92 (s, 3H); Calc. for $C_{26}H_{36}O_3$ C 78.74, H 9.15, found C 79.02, H 9.19.

Due to our previous experience [16,17] with this reaction for polyfunctional molecules, several reaction conditions were meticulously explored one of which lead to the desired product. Thus, $TiCl_3(DME)_{1.5}$ complex prepared with absolute reagents was combined with Zn-Cu in a glove-box, the resulting mixture was heated at reflux in absolute DME and **14** added over several hours via syringe pump [18]. After work-up and chromatography the desired **15** was isolated after HPLC purification (SiO_2 2% EtOAc-hexane) as an oil in 11% yield as an inseparable mixture of two diastereomeric benzylethers[9]. NOE investigations confirmed the Z-geometry of the newly formed double bond but during our NMR studies we also observed the slow but complete isomerization of the endocyclic double bond to the less strained exocyclic methylene position (**16**) in **15**. Thus, the successful McMurry coupling leading to the 11-membererd ring concludes the first synthesis of the trinervitane skeleton with correct relative stereochemistry and positioning of the unsaturated functionalities.

9) ^{1}H-NMR (400MHz, $CDCl_3$): δ 7.25-7.43 (m, 5H), 4.79 (ddd, 1H), 4.53 (m, 2H), 3.25 (m, 1H), 2.80 (dt, 1H), 2.58 (dt, 1H), 2.23 (m, 1H), 1.18-2.18 (m, 15H), 1.66 (bs, 3H), 1.38 (bs, 3H), 0.98 (s, 3H); MS (70eV) m/e 364 (M^+, 20).

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