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Enantioselective Total Synthesis of Nicandrenones

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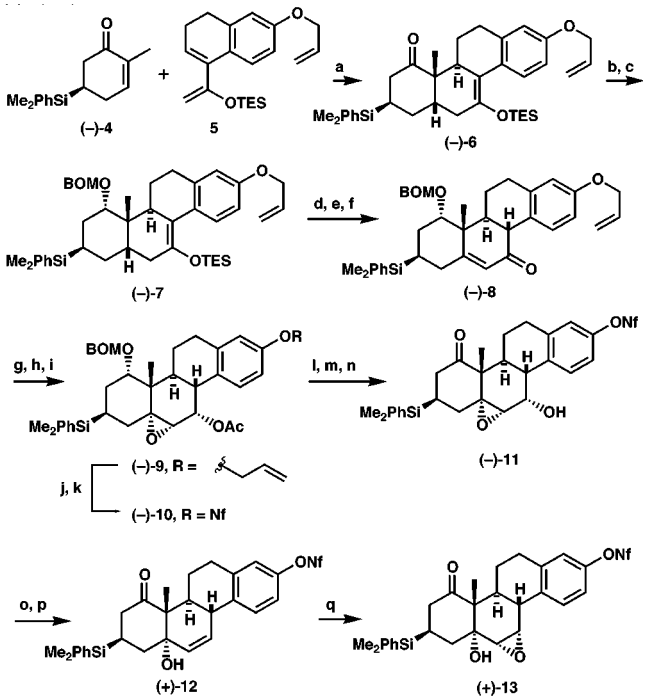
The nicandrenone (NIC) family of structurally complex, steroid-derived natural products includes the active principals of *Nicandra physaloides* (the Pyruvian "shoofly" plant) which give rise to its insect repellent and antifeedant properties.[1] The novel structures of the nicandrenones were elucidated independently by groups in the US[2] and UK[3] almost 30 years ago. The NIC family is structurally related to another and even larger class of plant products, the withanolides.[4] No member of either group has been made by total synthesis. We describe herein the first syntheses of nicandrenones, specifically NIC-1 lactone (**1**), NIC-1 (**2**), and NIC-10 (**3**), by an approach which is both enantio- and diastereoselective.

The synthesis of the tetracyclic nicandrenone nucleus (Scheme 1) commenced with a highly unusual *exo*-selective Diels−Alder reaction to generate all four rings in a stereocontrolled way. Addition of diene **5**[5] (1.05 equiv) to a mixture of the chiral α,β-enone **4**[6] and methylaluminum dichloride (1.05 equiv) in CH_2Cl_2 at −78 °C over 2.5 h resulted in formation of the *exo* adduct **6** (85%, *exo*−*endo* selectivity >15:1 by ^{1}H NMR analysis). The mechanistic basis of the high *exo* selectivity in the reaction leading to **6** has recently been analyzed in detail.[7,8] Conversion of **6** to the benzyloxymethyl (BOM) ether **7**[9] was accomplished in 82% overall yield by reduction with $LiAlH_4$ (1.05 equiv) in Et_2O at −78 °C for 20 min and subsequent reaction with BOM-Cl (2 equiv) and EtN(*i*-Pr)$_2$ in CH_2Cl_2 at 23 °C for 46 h. The α,β-enone **8**[9] was obtained from **7** in 64% overall yield by the following sequence: (1) TES cleavage with 0.6 equiv of *p*-toluenesulfonic acid in MeOH−CH_2Cl_2 at 23 °C for 5 min, (2) trimethylsilyl enol ether formation with LDA−TMSCl in THF at −78 °C, and (3) α,β-enone formation with 10 mol % Pd(OAc)$_2$ and O_2 in dimethyl sulfoxide (DMSO) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine at 23 °C for 12 h. The carbonyl group of **8** was reduced (L-selectride, THF, −78 °C, 20 min) and the resulting allylic alcohol was subjected to cis epoxidation (*t*-BuOOH, 0.3 equiv of VO(acac)$_2$, CH_2Cl_2, 0 °C, 20 h) and subsequent acetylation to give **9**[9] (71% from **8**). Deallylation of **9** (5 mol % Pd(Ph$_3$P)$_4$, excess Et_2NH, CH_2Cl_2, 3 h at 40 °C) and

Scheme 1



[a] $MeAlCl_2$, CH_2Cl_2, −78 °C. [b] $LiAlH_4$, Et_2O, −78 °C. [c] $C_6H_5CH_2OCH_2Cl$, EtN(*i*-Pr)$_2$, CH_2Cl_2, 23 °C. [d] *p*-TsOH, MeOH, 23 °C. [e] LDA, TMSCl, −78 °C. [f] Pd(OAc)$_2$, O_2, DMSO, 23 °C. [g] L-selectride, THF, −78 °C. [h] *t*-BuOOH, VO(acac)$_2$, CH_2Cl_2, 0 °C. [i] Ac_2O, Et_3N, DMAP, −25 °C. [j] Pd(Ph$_3$P)$_4$, Et_2NH, CH_2Cl_2, 40 °C. [k] $C_4F_9SO_2F$, Et_3N, CH_2Cl_2, 23 °C. [l] H_2, Pd−C, 23 °C. [m] Dess−Martin periodinane, CH_2Cl_2, 23 °C. [n] K_2CO_3, MeOH, 23 °C. [o] MgI_2, NaI, CH_2Cl_2−CH_3CN, 0 °C. [p] CH_3SO_2Cl, Et_3N, −60 to 23 °C. [q] *t*-BuOOH, VO(acac)$_2$, CH_2Cl_2, 0 °C.

reaction with nonafluorobutanesulfonyl fluoride (NfF) and Et_3N in CH_2Cl_2 for 18 h at 23 °C produced the nonaflate **10**[9] (93% from **9**). Epoxy ketone **11**[9] was accessed from **10** in 86% overall yield by the following sequence: (1) BOM ether cleavage (1 atm H_2, Pd−C, EtOAc−HOAc, 23 °C, 7 h), (2) Dess−Martin periodinane oxidation of the resulting alcohol (in CH_2Cl_2 at 23 °C for 2 h), and (3) deacetylation (K_2CO_3 in CH_3OH at 23 °C). The oxiranyl carbinol subunit of **11** was unusually reactive as demonstrated by transformation to the corresponding 6β-iodo-5,7-diol structure upon treatment with 6 equiv of MgI_2 and 6 equiv of NaI in CH_3CN−CH_2Cl_2 at 0 °C for 10 min. Reaction of this diol with CH_3SO_2Cl−Et_3N (2 equiv, 3 equiv) at −66 °C to +23 °C over 1.5 h resulted in elimination to form **12**[9] in 72% overall yield.[10,11] Epoxidation of **12** with *t*-BuOOH and 0.1 equiv of VO(acac)$_2$ in CH_2Cl_2 at 0 °C for 44 h gave **13**[9] in 76% yield.

The enantioselective synthesis of the NIC-1 side chain fragment is outlined in Scheme 2, the starting point being the known lactone **14**.[12] Amidation with a reagent from 2.5 equiv of trimethylaluminum and 2.5 equiv of *N*,*O*-dimethylhydroxylamine hydrochlo-

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(5) Diene **5** was synthesized from 6-allyloxy-1-tetralone by the following sequence: (1) addition of 1-ethoxyvinyllithium, (2) dehydration of the resulting tertiary alcohol, (3) hydrolysis of vinyl ether to methyl ketone, and (4) triethylsilyl (TES) enol ether formation using triethylsilyltriflate and triethylamine in CH_2Cl_2 at 0 °C.

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(8) The structure of adduct **6** (a racemic sample) was confirmed by reaction with $CuCl_2$ in dimethylformamide at 60 °C to form the corresponding Δ(8)-1,7-diketone (steroid numbering, mp 172−3 °C) and subsequent X-ray crystallographic analysis. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(9) This product was purified by column chromatography on silica gel.

(10) The formation of **12** from the 6β-iodo-5,7α-diol precursor is considered to occur via the 7α-mesylate by solvolysis to the 6,7-β-iodonium ion which undergoes I^+ transfer to Et_3N forming Et_3NI^+. The transfer of positve halogen to amines is well-known. For a similar elimination see: Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433.

(11) (a) Attempts to generate **12** by a Wharton elimination of 5,6-α-epoxy-7-keto intermediate with hydrazine were completely unsuccessful. See: Dupuy, C.; Luche, J. L. *Tetrahedron* **1989**, *45*, 3437. (b) For epoxidation reactions catalyzed by VO(acac)$_2$ see: Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(12) Lactone **14** was synthesized in two steps from 2,3-dimethylbutadiene as described by Aumann et al. (Aumann, R.; Ring, H.; Krüger, C.; Goddard, R. *Chem. Ber.* **1979**, *112*, 3644) using sequential monoepoxidation and Pd-catalyzed carbonylation.

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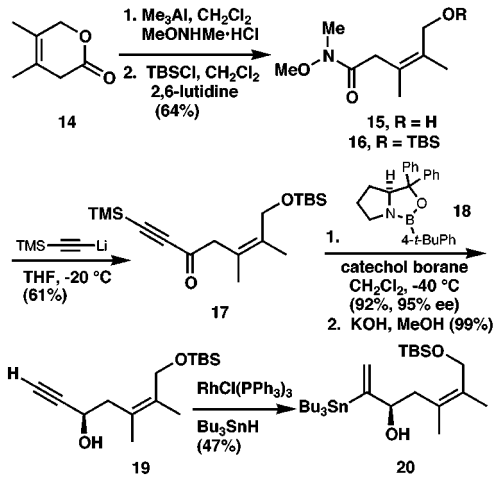
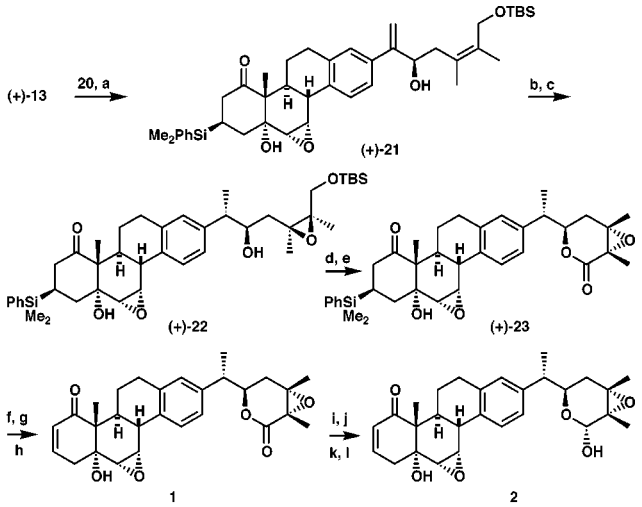
Scheme 2



ride[13] in CH_2Cl_2 at −5 °C for 30 min followed by silylation of the resulting hydroxy amide **15** (*tert*-butyldimethylsilyl chloride, 2,6-lutidine, CH_2Cl_2 at 0 °C for 10 min) provided the protected amide **16**[9] (64% from **14**). Ethynylation of **16** with lithium trimethylsilylacetylide (THF, −20 °C, 1 h) produced ynone **17**[9] (61%) which was subjected to CBS reduction[14] using 1.2 equiv of catechol borane and 5 mol % of oxazaborolidine **18**[15] in CH_2Cl_2 at −40 °C for 40 min to give after desilylation (KOH, CH_3OH, 23 °C, 10 min) the propargylic alcohol **19** in 92% yield and 95% ee.[9,16] Vinylstannane **20** was prepared by reaction of **19** with 1.5 equiv of tributyltin hydride and 0.1 equiv of $RhCl(PPh_3)_3$ at 23 °C for 20 h (47% yield).

The coupling of nonaflate **13** with vinylstannane **20** using the conditions recently developed for such difficult Stille reactions[17] (0.5 equiv of $Pd(Ph_3P)_4$, excess of CuCl, and excess of LiCl in dimethyl sulfoxide at 60 °C for 48 h) afforded **21**[9] in 74% yield. The completely diastereoselective transformation of **21** into the epoxide **22**[9] was effected in 88% overall yield by (1) reduction of terminal methylene with 1 atm of H_2 and 0.4 equiv of Rh(nbd)(dppb)BF_4[18] in CH_2Cl_2 at 0 °C for 48 h and (2) epoxidation with *t*-BuOOH and 0.1 equiv of $VO(acac)_2$ in CH_2Cl_2 at 0 °C for 2 h. Conversion of **22** to the epoxy lactone **23**[9] was carried out in 90% overall yield by (1) TBS ether cleavage (3 equiv of Bu_4NF in THF at 0 °C) and (2) oxidation with 3 equiv of NaOCl, 10 mol % KBr, and 5 mol % TEMPO (Aldrich Co.) in CH_2Cl_2−H_2O at 0 °C for 10 min. NIC-1 lactone (**1**) was obtained from **23** by (1) replacement of Me_2PhSi by hydroxyl using 5 equiv of $Hg(OAc)_2$ and CH_3CO_3H in HOAc at 23 °C for 3 h[19] and (2) β-elimination by acetylation (Ac_2O, Et_3N, DMAP at 23 °C) followed by treatment of the resulting β-acetoxy ketone with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 at 23 °C for 3 h. NIC-1 lactone (**1**) was converted into NIC-1 (**2**) by the following sequence: (1) reduction at both C(1) and lactone carbonyls by diisobutylaluminum hydride in toluene, (2) selective acetylation of the more reactive lactol hydroxyl by Ac_2O-Et_3N, (3) Dess−Martin oxidation at C(1), and (4) deacetylation (K_2CO_3−CH_3OH). Synthetic NIC-1 (**2**) was compared to authentic

Scheme 3

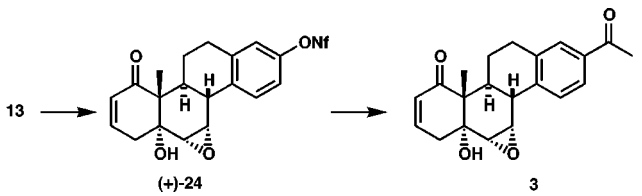


[a] cat. $Pd(Ph_3P)_4$, CuCl, LiCl, DMSO, 60 °C. [b] 1 atm H_2, Rh(nbd)Id-ppb)BF_4, 0 °C. [c] *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, 0 °C. [d] Bu_4NF, THF, 0 °C. [e] NaOCl, cat. TEMPO, cat. KBr, CH_2Cl_2, H_2O, 0 °C. [f] $Hg(OAC)_2$, AcOOH, AcOH, 23 °C. [g] Ac_2O, Et_3N, DMAP, CH_2Cl_2, 23 °C. [h] DBU, CH_2Cl_2, 23 °C. [i] DIBAL-H, CH_2Cl_2, −30 °C. [j] Ac_2O, Et_3N, 23 °C. [k] Dess−Martin periodinane, CH_2Cl_2, 40 °C. [l] K_2CO_3, MeOH, 0 °C.

samples[20] (500-MHz ^1H NMR, 100-MHz ^{13}C, IR, TLC, optical rotation, and mixed mp) and found to be indistinguishable.

The nonaflate **13** also provided ready access to NIC-10 (**3**) as shown in Scheme 4. Ring A hydroxy desilylation[19] and β-elimination via the acetate, as described in Scheme 3 for **23** → **1**, generated the α,β-enone **24** (92%).[9] Stille coupling of **24** with 1-ethoxyvinyltributylstannane, as described for **13** → **21**, afforded the corresponding tetracyclic 1-ethoxyvinyl ether, hydrolysis of which using 10 equiv of wet acetic acid in CH_2Cl_2 at 25 °C for 20 min provided NIC-10 (**3**),[9] as demonstrated by comparison with published physical data.

Scheme 4



Apart from establishing the first totally synthetic route to nicandrenones **1**−**3**, there are a number of noteworthy features of the synthesis described herein: (1) the remarkably powerful *exo*-selective Diels−Alder construction **4** + **5** → **6**, (2) the emplacement of the complex pattern of functionality of the A and B rings, (3) the development of new conditions for the otherwise unworkable coupling **13** + **20** → **21**, and (4) the simple elaboration of the complex side chain.

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Supporting Information Available: Supplemental procedures for synthetic intermediates (PDF). A crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Enantioselectivity was determined by HPLC analysis of the *p*-nitrobenzoate derivative of the TMS derivative of **19**, using a Whelk-O1 column, 0.2% 2-propanol in hexane, and a flow rate of 0.25 mL/min.
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