Enantioselective Total Synthesis of (-)-Strychnine[1]

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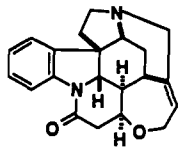
Strychnine (**1**) has played a vital role in the development of natural products chemistry. First isolated in 1818 from *Strychnos ignatii* by Pelletier and Caventou, strychnine was among the first plant alkaloids obtained in pure form. After decades of inves-

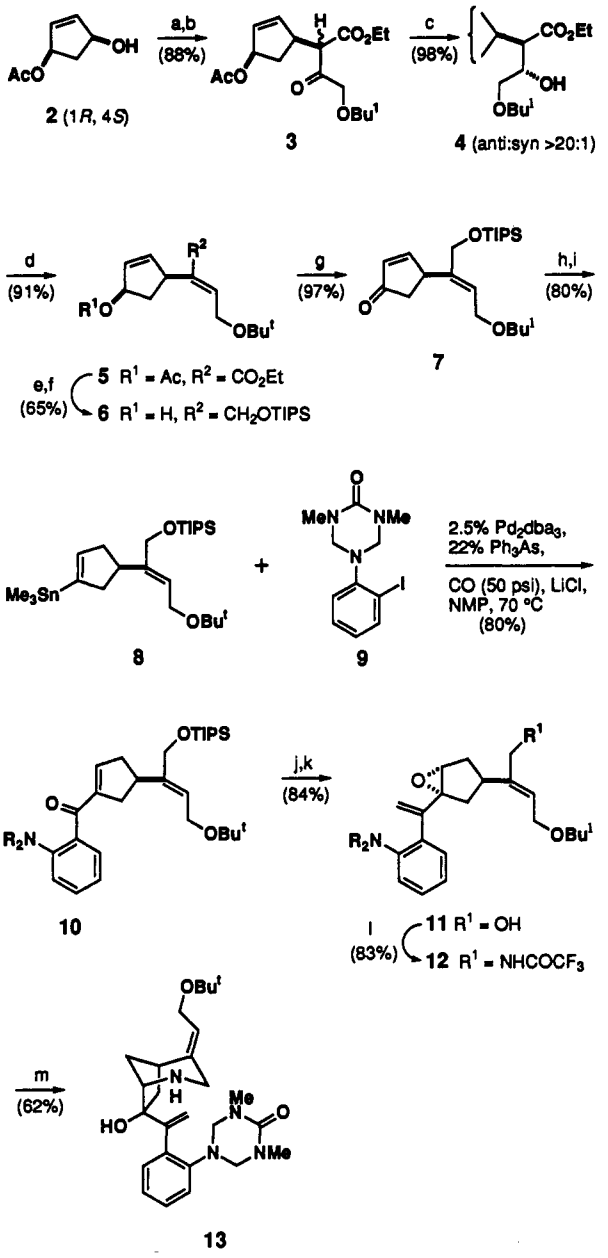


(-)-Strychnine (**1**)

tigation, the structural elucidation of strychnine in 1946 represented one of the crowning accomplishments of classical structural chemistry.[3,4] Its total synthesis by Woodward only 8 years later was an achievement of even greater significance, since prior to this feat no compound approaching the complexity of strychnine had been prepared by chemical synthesis.[5] That strychnine's seven rings displayed on only 24 skeletal atoms still represents a formidable challenge for total synthesis is apparent in the fact that only last year was a second total synthesis of strychnine published by Magnus and co-workers.[6] This synthesis, like the pioneering Woodward synthesis, involved intersection with an intermediate available by degradation of strychnine.[5,6] Most recently, two syntheses of (±)-strychnine have been communicated by the groups of Stork[7] and Kuehne.[8] Herein we report the first asymmetric total synthesis of (-)-strychnine. This highly efficient total synthesis features the use of the cationic aza-Cope–Mannich reaction to assemble the pentacyclic strychnan core.[9,10]

The preparation in enantiopure form of the unsaturated azabicyclo[3.2.1]octane **13**, the key aza-Cope–Mannich rearrangement substrate, is summarized in Scheme I. The sequence begins with (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate (**2**), which is available in high enantiomeric purity on a large scale from the hydrolysis of *cis*-1,4-diacetoxycyclopent-2-ene with

Scheme I [a]



[a] Reaction conditions: (a) MeOCOCl, pyridine, CH_2Cl_2, 23 °C, 97%; (b) $Bu^tOCH_2COCH_2CO_2Et$, NaH, 1% $Pd_2(dba)_3$, 15% PPh_3, THF, 23 °C, 91%; (c) $NaCNBH_3$, $TiCl_4$, THF, –78 °C; (d) DCC, CuCl, benzene, 80 °C; (e) DIBAL, CH_2Cl_2, –78 °C, 98%; (f) TIPSCl, tetramethylguanidine, NMP, –10 °C; (g) Jones oxidation, acetone, –5 °C; (h) L-Selectride, $PhNTf_2$, THF, –78 → 0 °C, 88%; (i) Me_6Sn_2, 10% $Pd(PPh_3)_4$, LiCl, THF, 60 °C, 81%; (j) *t*-BuO_2H, Triton-B, THF, –15 °C, 91%; (k) $Ph_3P{=}CH_2$, THF, 0 → 23 °C, 92%; TBAF, THF, –15 °C, 100%; (l) MsCl, *i*-Pr_2NEt, CH_2Cl_2, –23 °C; LiCl, DMF, 23 °C; NH_2COCF_3, NaH, DMF, 23 °C; (m) NaH, benzene, 100 °C; KOH, EtOH–H_2O, 60 °C. R_2N = 1,3-dimethylhexahydro-2-oxo-1,3,5-triazinyl.

electric eel acetylcholinesterase.[11] Reaction of **2** with methyl chloroformate, followed by selective palladium-catalyzed displacement of the allylic carbonate derivative[12,13] with sodium ethyl α-*tert*-butoxyacetoacetate[14] provided the *cis*-adduct **3** (a

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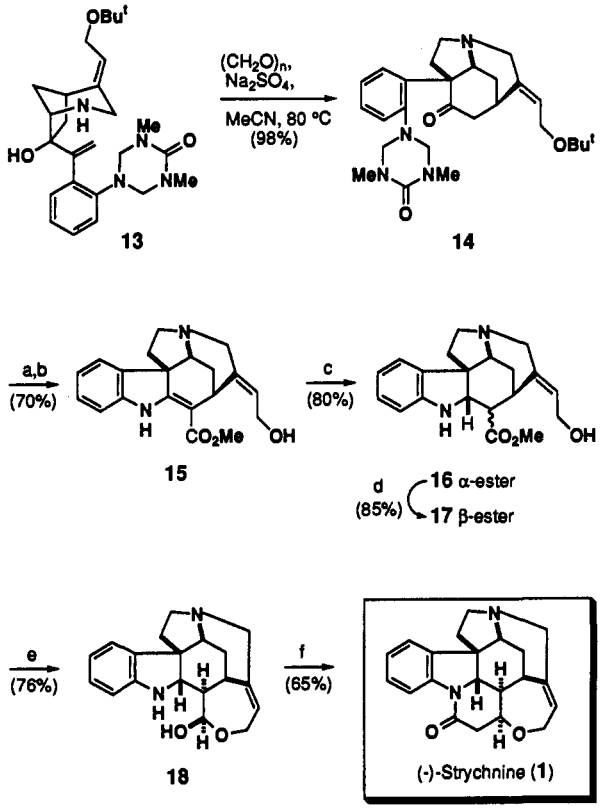
1:1 mixture of diastereomers) in 88% yield.[15] Stereocontrolled reduction of **3** with Felkin–Ahn selectivity was best realized by reaction in THF at −78 °C with excess $NaCNBH_3$ in the presence of 1.1 equiv of $TiCl_4$.[16] This treatment converted both diastereomers of **3** to the corresponding *anti* β-hydroxy esters **4** (stereoselectivity >20:1) in nearly quantitative yield. Direct *syn* dehydration[17] of this mixture afforded, after chromatographic removal of 2–3% of the unwanted (*Z*) stereoisomer, the (*E*)-butenoate **5** in 89% overall yield from **3**.[18,19] Reduction of **5** with excess *i*-Bu_2AlH provided the corresponding diol, which was selectively protected by careful treatment with triisopropylsilyl chloride and 1,1,3,3-tetramethylguanidine[20] at −10 °C in *N*-methyl-2-pyrrolidone to give **6** in 65% yield. Jones oxidation of **6** at −5 °C then provided cyclopentenone **7** in 97% yield.

Regioselective conversion of cyclopentenone **7** to the enol triflate derivative,[21] followed by palladium-catalyzed coupling of this intermediate with hexamethylditin,[22] provided vinylstannane **8** in 80% yield. Using conditions we had recently optimized for a related transformation,[10] palladium-catalyzed carbonylative coupling of **8** with the triazone-protected *ortho*-iodoaniline **9**[23] was accomplished in 80% yield to afford enone **10**.[24] At this stage, the enantiomeric purity of **10** was confirmed to be >95% ee by ^1H NMR analysis of the α-methoxyphenylacetic esters prepared by cleavage of the TIPS ether (*n*-Bu_4NF) of **10** and subsequent acylation (DCC, DMAP) of the liberated primary alcohol with (*R*)- or (*S*)-α-methoxyphenylacetic acid.[25] The azabicyclooctane ring system was next assembled from **10** by stereoselective epoxidation, followed by Wittig methylenation and desilylation to afford **11**. Conversion of this intermediate to the allylic trifluoroacetamide **12**, followed by cyclization with NaH in benzene at 100 °C[10,26] and final removal of the trifluoroacetyl group with KOH, provided azabicyclooctane **13** in 43% overall yield from enone **10**.

The crucial aza-Cope–Mannich reorganization was accomplished in *essentially quantitative yield* by heating **13** in acetonitrile with excess paraformaldehyde and anhydrous Na_2SO_4 to provide the highly crystalline pentacyclic diamine **14** (98% yield from an 800-mg scale reaction) (Scheme II). Acylation of **14** with methyl cyanoformate,[27] followed by treatment of the β-ketoester with 5% HCl in refluxing methanol, provided **15** (18-hydroxyakuammicine) in 70% yield. Reduction of this intermediate with Zn dust in acidic MeOH resulted in saturation of the vinylogous carbamate functionality from the β-face to afford **16**.[28] Base-promoted epimerization of this intermediate provided the known β-ester **17**,[28] which was reduced at −78 °C in CH_2Cl_2 with *i*-Bu_2AlH to provide, in 52% overall yield from **15**, Wieland–Gumlich aldehyde **18**.[29] Finally, reaction of **18** with malonic acid and acetic anhydride, as described earlier by Anet and Robinson,[30] led to (−)-strychnine in 65% yield: mp 278–285 °C (EtOH), mixture mp 278–285 °C, lit.[5] mp 275–285 °C; $[\alpha]^{25}_D$ −139° (*c* = 0.4, $CHCl_3$), lit.[30] $[\alpha]^{25}_D$ −139° (*c* = 1.0, $CHCl_3$).

Scheme II [a]



[a] Reaction conditions: (a) LDA, $NCCO_2Me$, THF, −78 °C; (b) 5% HCl–MeOH, reflux; (c) Zn dust, 10% H_2SO_4–MeOH, reflux; (d) NaOMe, MeOH, 23 °C; (e) *i*-Bu_2AlH, $CHCl_2$, −78 °C; (f) $CH_2(CO_2H)_2$, Ac_2O, NaOAc, HOAc, 110 °C.[31]

The first asymmetric total synthesis of strychnine has been accomplished in 20 steps and ~3% overall yield from the readily available[11] enantiopure hydroxy cyclopentenyl acetate **2**. The efficiency of this total synthesis, which is several orders of magnitude more efficient than the two previously published strychnine syntheses,[5,6] provides an important benchmark of the power of the aza-Cope rearrangement–Mannich reaction to solve formidable problems in alkaloid construction. The latent symmetry of **2**,[13] moreover, should allow this total synthesis strategy to be directly extended to the preparation of *ent*-strychnine.[31]

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Supplementary Material Available: Characterization data for key intermediates and copies of ^1H and ^{13}C NMR spectra of synthetic (−)-strychnine (7 pages). Ordering information is given on any current masthead page.

(15) Intermediates were fully characterized by ^1H and ^{13}C NMR, IR, and MS analyses. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. Unless noted otherwise, yields refer to purified products.

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