COMMUNICATION

Reserpine synthesis: a protocol for the stereoselective construction of the densely functionalized ring-E

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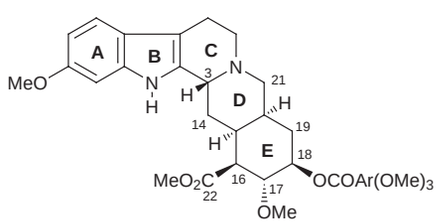
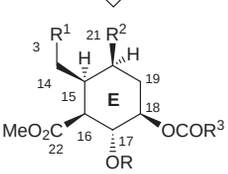
A new approach to densely functionalized cyclohexanoid derivative 12, embodying the complete stereochemical pattern of ring-E of the complex indole alkaloid reserpine 1, from a readily available tricyclo[5.2.1.0^{2,6}]decane precursor 5 is described.

Reserpine **1**, first isolated from the Indian snake root, *Rauwolfia serpentina* Benth, is a prominent member of the yohimbine group of alkaloids and notable for its complex architecture and clinical use in the treatment of hypertension and mental disorders. While the first synthesis of reserpine was accomplished in a landmark effort by Woodward *et al.*[1a] over forty years ago, the challenge associated with the construction of the pentacyclic frame of **1**, replete with six stereogenic centers, continues to engage the attention of synthetic chemists.[1,2] The main concern in the synthesis of **1** has been the generation of stereochemistry and functionalization pattern of ring-E *e.g.* **2**,[1,2] wherein five of its six stereogenic centers are located.



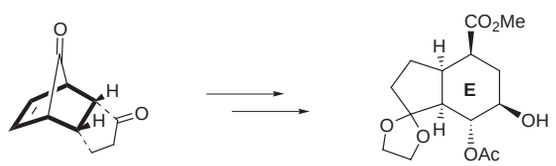
1



R = H, Me, Ac
R^1= R^2= CO_2Me, CHO *etc.*
R^3= $Ar(OMe)_3$

2

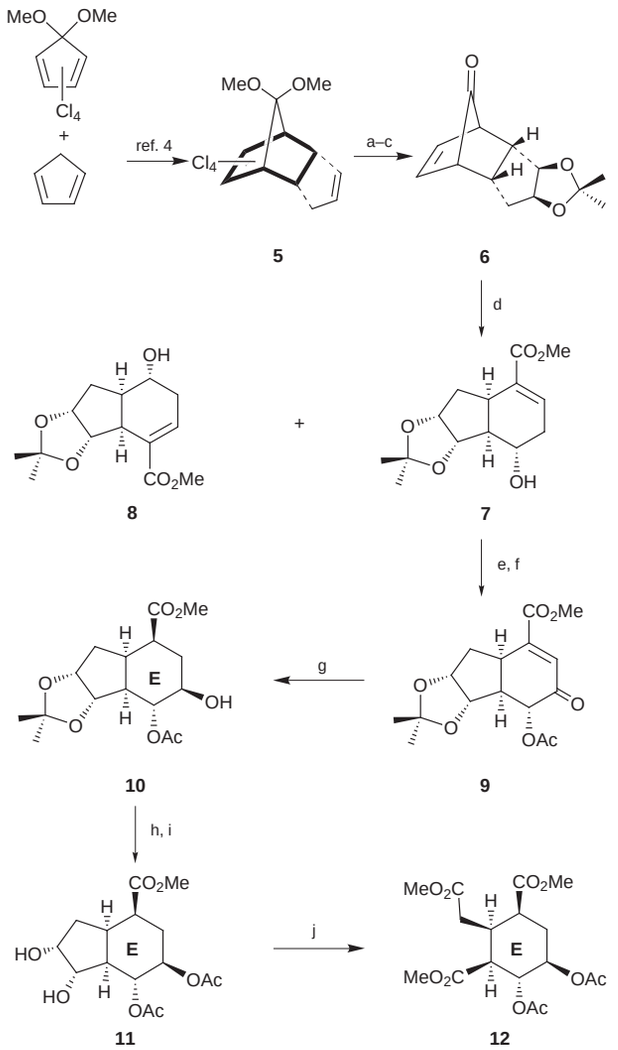
Several novel and interesting solutions to ring-E construction have been presented en route to the synthesis of **1**.[2,3] We have visualized an approach to the densely functionalized ring-E of reserpine from *endo*-tricyclo[5.2.1.0^{2,6}]decane precursors, whose key feature is the retrieval of the six-membered ring (see bold portion of **3**), locked within its tricyclic framework. In pursuit of this objective, we have recently reported[3] the elaboration of *endo*-tricyclo[5.2.1.0^{2,6}]decane derivative **3** to the bicyclic hydrindane **4** in which a regioselective Haller–Bauer cleavage served as the pivotal step for opening the norbornyl bridge. The six-membered ring in **4** had all the requisite stereochemical features present in the ring-E of reserpine. However, a trivial step like deketalisation in **4**, quite unexpectedly proved capricious and thwarted further attempts towards the extraction of the ring-E from it. Overcoming this impediment necessitated the selection of a new starting material, recourse to a different tactic to open the norbornyl bridge and adoption of a different regime of functional group transformations. We now report that the readily accessible[4] Diels–Alder adduct **5**, obtainable from two commercially available cyclopentadienes, can be successfully elaborated through stereocontrolled manipulation of functionalities to generate the requisite substitution pattern present in ring-E *e.g.* **2**.



3 **4**

The *endo*-adduct **5**,[4] obtained through Diels–Alder reaction between 5,5-dimethoxytetrachlorocyclopentadiene and cyclopenta-1,3-diene, on regioselective *cis*-dihydroxylation at the distal disubstituted double bond, exhaustive reductive dehalogenation and single-pot acid catalyzed acetal-deprotection and 1,2-diol-protection furnished the ketoacetonide **6**,† quite satisfactorily, Scheme 1. The bridging carbon in the tricyclic compound **6** was advantageously removed through Baeyer–Villiger oxidation, which furnished a mixture of regioisomeric lactones (55:45). Methanolysis of these lactones led to concomitant double bond isomerization and a readily separable

† All new compounds reported here were characterized on the basis of complementary spectral data (IR, ^{1}H and ^{13}C NMR, elemental analysis). When appropriate, ^{1}H-^{1}H COSY and DEPT experiments were employed to delineate the stereostructures. Selected spectral data: **6**: δ_H(200 MHz, $CDCl_3$) 6.54–6.51 (m, 2H), 4.39 (m, 1H), 4.17 (m, 1H), 3.30–2.70 (series of m, 4H), 2.20–2.00 (m, 1H), 1.60–1.55 (m, 1H), 1.47 (s, 3H), 1.26 (s, 3H); δ_C(50.0 MHz, $CDCl_3$) 202.2, 133.0, 132.0, 110.8, 84.3, 83.4, 52.0, 50.2, 48.5, 42.2, 35.0, 27.9, 25.4. **9**: δ_H(200 MHz, $CDCl_3$) 6.78 (s, 1H), 5.18 (d, 1H, *J* 13.6 Hz), 4.86 (t, 1H, *J* 5.2 Hz), 4.46 (d, 1H, *J* 5.6 Hz), 3.86 (s, 3H), 3.70–3.50 (m, 1H), 2.78 (dd, 1H, *J* 7, 6 Hz), 2.57 (dd, 1H, *J* 7.5, 6 Hz), 2.25 (s, 3H), 1.81 (m, 1H), 1.50 (s, 3H), 1.32 (s, 3H); δ_C(50.0 MHz, $CDCl_3$) 192.8, 170.5, 165.6, 148.6, 131.1, 109.8, 81.9, 80.6, 71.1, 52.8, 50.2, 37.5, 37.1, 26.1, 23.7, 20.6. **10**: δ_H(200 MHz, $CDCl_3$) 4.73 (m, 1H), 4.50 (t, 1H, *J* 10 Hz), 4.32 (d, 1H, *J* 5.8 Hz), 3.70 (s, 3H), 3.56 (m, 1H), 2.90–2.75 (m, 2H), 2.17 (s, 3H), 2.19–1.62 (series of m, 5H), 1.45 (s, 3H), 1.27 (s, 3H); δ_C(50.0 MHz, $CDCl_3$) 173.2, 172.2, 109.2, 82.0, 79.3, 74.1, 72.2, 51.8, 50.1, 39.8, 36.9, 32.0, 30.3, 25.9, 23.6, 21.1. **12**: δ_H(200 MHz, $CDCl_3$) 5.38 (dd, 1H, *J* 11.8, 9.8 Hz), 4.81 (ddd, 1H, *J* 11.8, 9.8, 5.2 Hz), 3.67 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.28 (m, 1H), 2.83 (dd, 1H, *J* 11.6, 4 Hz), 2.74 (dt, 1H, J_1 14, J_2 4 Hz), 2.45 (ABq, 2H, *J* 17.4, 6.6, 17.4, 5 Hz), 2.23 (dt, 1H, J_1 12.6 Hz, J_2 4 Hz), 2.02 (s, 3H), 1.97 (s, 3H), 1.75 (dt, 1H, J_1 25.4 Hz, J_2 11.2 Hz); δ_C(50.0 MHz, $CDCl_3$) 171.9 (2C), 170.4, 170.3, 169.4, 72.8, 69.4, 52.2 (2C), 51.8, 49.8, 43.8, 34.3, 30.2, 27.4, 20.9, 20.7.



Scheme 1 *Reagents and conditions*: (a) OsO_4, Me_2CO–H_2O–Bu^{t}OH (5:3:1), 24 h, 90%; (b) Na/liq. NH_3, THF, 15 min, 50%; (c) Me_2CO, Amberlyst-15, 6 h, 83%; (d) MCPBA, DCM, 30 min; KOH, MeOH, 20 min, 60–65%; (e) Ac_2O, Py, 2 h, 95%; (f) PDC, Bu^{t}OOH, Celite, C_6H_6, 2 H, 30–40%; (g) H_2 10% Pd/C, EtOAc, 65%; (h) Ac_2O, Py, 2 h, 95%; (i) aq. AcOH, Δ, 15 min, 80%; (j) $NaIO_4$, aq. THF, 10 min; Jones oxidation, Me_2CO, 10 min; CH_2N_2–Et_2O, 20%

mixture of hydroxy esters **7** and **8** was obtained. The two hydroxy esters **7** and **8** could be readily distinguished through an incisive analysis of their ^{1}H-^{1}H COSY spectra. The desired hydroxy ester **7** was acetylated and subjected to allylic oxidation[5] to yield the desired enone **9**. Catalytic hydrogenation in **9** proceeded with high stereoselectivity, from the convex *exo*-face, and both the conjugated and the carbonyl double bonds were reduced to furnish the hydroxy ester **10**. Thus, the requisite stereochemistry in the cyclohexane ring, corresponding to the natural product, was readily installed. The hydroxy group in **10** was further acetylated and the acetonide group was deprotected to furnish the diol diacetate **11** with well-defined stereochemistry at seven contiguous carbon centers on a *cis*-hydrindane skeleton. Exposure of **11** to periodate, followed by Jones oxidation and esterification led to the projected, densely functionalized triester **12** (*cf.* **2**), whose proton NMR data revealed ^{1}H-^{1}H coupling constants in conformity with its stereochemistry.[5] Our triester **12** is a close functional group variant of the ring-E intermediates *e.g.* **2**, employed earlier by Woodward [1a] and Stork [1e] and others [1b,g] for the synthesis of reserpine **1**.

In summary, we have developed a new, simple access to the ring-E segment of reserpine **1**, fully embellished with functionalities and stereochemical features present in the natural product, from a readily available starting material.

Experimental

Preparation of hydroxy esters 7 and 8

To an ice-cold suspension of tricyclic ketone **6** (2.2 g, 10 mmol) and anhydrous Na_2CO_3 (1.1 g, 10.3 mmol) in dry dichloromethane (25 ml), *m*-chloroperbenzoic acid (2.7 g, 15.6 mmol) was added and the reaction mixture was stirred for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and the contents were stirred for another 15 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (25 ml × 2). The combined organic extracts were again washed with saturated aqueous $NaHCO_3$, followed by water and brine. The crude mixture of lactones (~2.4 g) obtained after the removal of the solvent was dissolved in dry methanol (10 ml) and a small pellet of KOH was added. The contents were then stirred for 20 min at room temperature. After the removal of methanol under vacuum, the reaction mixture was diluted with water and extracted with diethyl ether (25 ml × 2). The organic layer was washed with water and dried. The crude residue (~2 g) obtained after the removal of the solvent was charged on a silica gel column and eluted with 20% ethyl acetate–hexane to furnish the hydroxy esters **7** (925 mg) and **8** (810 mg) in 63% overall yield in 55:45 ratio. **7**: ν_{max}(neat)/cm^{-1} 3445, 1715, 1647, 1263, 1087, 750; δ_H(200 MHz, $CDCl_3$) 6.84 (m, 1H), 4.85 (d, 1H, *J* 5.6 Hz), 4.70 (t, 1H, *J* 5.2 Hz), 3.74 (s, 3H), 3.60–3.20 (m, 2H), 2.64 (dt, 1H, J_1 18.4 Hz, J_2 5.8 Hz), 2.42 (dd, 1H, *J* 14, 6.6 Hz), 2.16 (m, 1H), 2.02 (dd, 1H, *J* 11.4, 6.6 Hz), 1.48 (s, 3H), 1.32 (m, 1H), 1.31 (s, 3H); δ_C(50.0 MHz, $CDCl_3$) 166.9, 136.4, 132.5, 109.4, 81.9, 79.9, 64.4, 52.1, 51.6, 39.3, 37.2, 35.4, 26.3, 23.9 (Found: C, 62.63; H, 7.53. Calc. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51%). **8**: ν_{max}(neat)/cm^{-1} 3439, 1715, 1647, 1259, 1047, 748; δ_H(200 MHz, $CDCl_3$) 6.87 (m, 1H), 4.57 (m, 2H), 4.05 (m, 1H), 3.78 (s, 3H), 3.05 (m, 1H), 2.80 (m, 1H), 2.39 (m, 2H), 1.92 (dd, 1H, *J* 13.6, 5.8 Hz), 1.49 (s, 3H), 1.35 (m, 1H), 1.30 (s, 3H); δ_C(50.0 MHz, $CDCl_3$) 167.1, 136.4, 129.3, 109.8, 84.7, 79.0, 65.3, 51.7, 42.6, 41.0, 34.5, 30.3, 26.4, 24.1 (Found: C, 62.68; H, 7.54. Calc. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51%).

Acknowledgements

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