A new synthetic approach to a functionally and stereochemically embellished cyclohexanoid, corresponding to the Woodward’s ring-E precursor 24 of the complex indole alkaloid reserpine 1 is delineated. Our scheme emanates from a readily available endo-tricyclo[5.2.1.0²⁶]decane system from which cis-hydrindane and cyclohexanoid moieties are sequentially extracted. The strategy outlined here exploits the propensity of the endo-tricyclo[5.2.1.0²⁶]decane and cis-hydrindane systems to react from the convex face to generate the requisite stereochemical pattern. Since 24 has been previously elaborated to the natural product, the present effort constitutes a formal synthesis of rac-reserpine.

The pentacyclic indole alkaloid reserpine 1, first isolated from the Indian snake root, *Rauwolfia serpentina* Benth, occupies a historically important position among natural products for a variety of reasons. Besides having a complex structure, 1 was among the very first few natural products to have been used clinically. For quite some time, reserpine 1 was commonly employed for the treatment of hypertension and mental disorders. The pentacyclic framework of reserpine 1 with six stereogenic centres and ample functionalisation was considered as a major synthetic challenge in the 1950’s and 1960’s. Its first synthesis by Woodward, nearly forty years ago, was a landmark and ranks among the classics of modern organic synthesis. Over the years, reserpine has continued to sustain the interest and attention of synthetic chemists and as many as eight total syntheses have been recorded to date. The approaches adopted towards the successful syntheses of 1 fall into two broad categories. In the first group are the approaches that focus on the construction of ring E of reserpine wherein five of the six stereogenic centres and much of the functionality reside. The original Woodward approach and those of Pearlman, Stork, Fraser-Reid, Liao and Hanessian have targeted an appropriately functionalised ring-E precursor 2 in which the requisite stereochemistry is built in. Woodward employed the Diels–Alder adduct of vinylacrylic acid and benzoquinone as the starting material in which a series of clever functional group manipulations were orchestrated to attain the ring-E stereochemistry. Intramolecular [2 + 2] photocycloaddition in a cyclohexene derivative and cyclobutane fragmentation was the stratagem employed by Pearlman in accessing ring E of 1. Stork et al. and Liao et al. employed the bicyclo[2.2.2]octane scaffold to deliver the desired stereochemistry of ring E. Fraser-Reid and Hanessian employed glucose and quinic acid, respectively, as chirons in their approach to reserpine 1.

On the other hand, Wender et al. and Martin et al. in their successful synthesis of reserpine have focused on assembling a cis-hydroisouquinoline moiety, incorporating the DE-rings of the natural product, employing Diels–Alder/Cope rearrangement and intramolecular Diels–Alder reaction as the key steps, respectively. In both, the E-ring as well as DE-ring approaches, appropriately constructed precursors 2 and 3 are condensed with indole derived AB-ring partners 4 and 5, respectively, to generate the pentacyclic framework of reserpine 1, Scheme 1.

Several innovative and interesting solutions to ring-E construction have been presented *en route* to the synthesis of 1. We have conceptualised a new approach to Woodward’s ring-E precursor of reserpine 1 from readily accessible endo-tricyclo[5.2.1.0²⁶]decane 6. The key feature of this strategy is the retrieval of the six-membered ring (see bold portion in 6) embedded within the tricyclic frame of 6. Another distinctive aspect of this approach is that all the ten carbon atoms of Woodward’s ring-E intermediate (see 8) are present in the tricyclic framework 6, which in turn is assembled from two $C_5$...
cyclopentadiene units (vide infra). Thus, no carbon needs to be added or removed from the tricyclic precursor 6, only skeletal restructuring and functional group changes are required. In practical terms, elaboration of 6 to 8 requires opening-up of the bridge (6→7), functional group adjustment as called for and finally oxidative cleavage of the double bond in 7 to deliver the ring-E intermediate 8. A particularly attractive feature of our simple approach is that both endo-tricyclic system 6 and the cis-hydrindane 7 are amenable to stereochemical control through their skeletal topology, with reagent addition expected to occur only from the exocentric face of the molecule. We report here the successful execution of the approach towards Woodward’s ring-E intermediate 9 as shown in Scheme 2, which in a formal sense constitutes a new synthesis of rac-reserpine 1.

Our approach emanated from two abundantly available C₃ building blocks, cyclopentadiene and 5,5-dimethoxytetra-chlorocyclopentadiene 10, which readily enter into Diels–Alder reaction to furnish the known tricyclic endo-adduct 11.⁶ The first priority was to protect the distal disubstituted cyclopentene double bond in a manner that at an appropriate stage it could be oxidatively cleaved to generate the cis disposed substitute at C15 and C16 (reserpine numbering) on the E-ring of 1. Regioselective, catalytic cis-dihydroxylation of 11 led to the tricyclic exo,exo-diol 12 which was directly subjected to exhaustive reductive dehalogenation in metal–ammonia solution to furnish 13. Exposure of 13 to acetonate in the presence of Amberlyst-15 resulted in the two desired protection–deprotection events taking place in a single-pot reaction. While the cis-diol moiety was protected as the acetonide derivative, the dimethyl acetal was deprotected to give keto-acetonide 14. Scheme 3. The stage was now set for the removal of the carbonyl bearing bridge in 14 to unravel the hydrindane framework. This was accomplished via Baeyer–Villiger (BV) oxidation. Reaction of 14 with m-chloroperbenzoic acid and methanolysis of the resulting lactones led to the formation of regioisomeric hydroxy esters 15 and 16 in a 55:45 ratio, Scheme 3. Apparently, the distal acetonide group in 14 has very little effect on the regiochemistry of BV oxidation and nearly equal amounts of 15 and 16 are obtained. The two esters 15 and 16 are readily separable and could be distinguished through an incisive analysis of their ¹H–¹H COSY spectra derived connectivities as depicted in Fig. 1. Although the lack of BV oxidation regioselectivity in 14 was a somewhat unsatisfactory outcome, the redeeming feature was the desired migration of the olefinic bond into conjugation with the ester moieties in 15 and 16 during methanolysis. This was considered necessary to recreate the correct stereochemistry at the ester bearing carbon centre (C20 of reserpine), taking advantage of the topology of the cis-hydrindane framework.

The free hydroxy group in the required regioisomer 15 was methylated employing methyl iodide and solid KOH under solvent free conditions⁷ to furnish the methoxy ester 17. It was now proposed to functionalise the allylic position in the ester 17 to generate the C18 centre of reserpine 1 present in ring E. Several reagents like Cr(CO)₃–t-BuOOH,⁸ CrO₃–dimethylpyrazole,⁹ CrO₃–AcOH,⁹a SeO₂–(cat)–t-BuOOH⁹b etc. were tried to oxidise 17 to the α,β-unsaturated enone 18 but none of them proved to be entirely satisfactory. Best results were obtained with PDC on Celite in the presence of tert-butyl hydroperoxide and 18 was obtained in ~30% yield.⁹b Scheme 4. Luche reduction⁸ of the enone carbonyl in 18 proceeded stereoselectively in an expected fashion to furnish 19. The hydride addition to the carbonyl group in 18 was from the convex face of the cis-hydrindane moiety and the correct stereochemistry corresponding to the C20 centre of reserpine was established. The next key step was to set the stereochemistry of the methoxy carbonyl bearing centre and towards that end the double bond in 19 was subjected to catalytic hydrogenation. The reduction was fairly stereoselective and an 85:15 mixture of epi-
mers 20 was obtained. The major epimer formed during the reduction of 19 was the α-isomer with enol-methoxycarbonyl group corresponding to the required C20-stereochemistry in 1. The separation of epimers 20 proved difficult at this stage and therefore we proceeded further as such towards the Woodward’s intermediate. DIBAL-H reduction of 20 to the aldehyde 21 and Wittig olefination furnished 22. The Wittig olefination was necessitated by our intent to protect the aldehyde functionality in 21 during subsequent steps. It was reasoned that the aldehyde functionality, which is present in the target structure could be readily regenerated at an appropriate stage from the olefin. As 22 turned out to be a nice solid, crystallization led to ready purification and it was obtained as a single stereoisomer and fully characterized. The secondary hydroxy group in 22 was now acetylated to 23. The final manoeuvre now was the unraveling of the cis disposed methoxycarbonyl and acetic acid side arms on the E-ring, corresponding to C16 and C15 of reserpine, respectively, from the five members ring of the cis-hydrindane 23. A four step sequence consisting of acetonide deprotection, periodate cleavage of the resultant dial to dialdehyde, Jones oxidation to the dicarboxylic acid and diazomethane esterification led to the diester 24 in modest yield, Scheme 4. The diester 24 has been recently reported by Fraser-Reid et al. and our synthetic sample was found to be identical with their sample in all respects. On ozonolysis, the olefinic moiety in 24 is readily transformed to the aldehyde functionality and the resulting product is the Woodward’s reserpine precursor 9, which has been earlier elaborated to the natural product.

In short, we have outlined a new approach to a densely functionalised cyclohexanoid, identical with Woodward’s ring-E intermediate from readily available cyclopentadiene based building-blocks. Our approach, notable for its conceptual simplicity, relies on the topology of the endo-tricyclo[5.2.1.0²⁶]decane and cis-hydrindane ring systems to achieve the desired stereoselectivity.

**Experimental**

**General**

Melting points were recorded on a Büchi SMP-20 apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer model 1310 or JASCO FT-IR. Solid samples were recorded as KBr pellets and liquids as thin films. ¹H NMR spectra were recorded at 200 MHz or 300 MHz and ¹³C NMR spectra were recorded at 50 MHz or 75 MHz on Bruker AC 200 or JNM-300 spectrometers respectively. ¹H and ¹³C NMR samples were made in CDCl₃ solvent and chemical shifts are reported on the δ scale using tetramethylsilane (Me₄Si) as the internal standard. J values are given in Hz. The standard abbreviations br, s, d, t, q and m refer to broad, singlet, doublet, triplet, quartet and multiplet, respectively. Mass spectra measurements were carried out on a JEOL JMS DX-303 spectrometer. Elemental analyses were carried out using a Perkin-Elmer 240C elemental analyzer or Carlo Erba 1106-CHN analyzer. Analytical thin-layer chromatography (TLC) was performed on (100×200) mesh) and ethyl acetate–hexane was used as eluent. Moisture sensitive reactions were performed using standard syringe-septum techniques under a nitrogen atmosphere. All solvents were distilled over appropriate drying agents, prior to use. Yields reported are isolated yields of materials judged homogeneous by TLC and NMR.

**Scheme 4** Reagents and conditions: (a) KOH, MeI, 20 h, 90%; (b) PDC, i-PrO₂O, Cellite, benzene, 1 h, 30%; (c) NaBH₄, CeCl₃·7H₂O, MeOH, −20 °C, 15 min; 62%; (d) H₂, Pd/C, EtOH, 1 h; (e) DIBAL-H, DCM, −78 °C; 30 min; (f) MePh₃P=CH₂, n-BuLi, 15 min, 48% (for 3 steps); (g) Ac₂O, pyridine, DMAP, 2 h, 86%; (h) 30% TFA, 1 h; NaOAc, 10% aq. THF; 15 min; Jones oxidation, Me₂CO; CH₂N₂, ether, 21% (for 4 steps).
In a 1:1 three necked round bottomed flask fitted with a condenser, KOH guard tube and a septum, 600 ml of distilled liquid ammonia was taken and a solution of diol 12 (18.2 g, 50 mmol) in 80 ml dry THF and 8 ml of dry ethanol were added. Small pieces of freshly cut sodium were slowly added to the reaction mixture with stirring till blue color persisted. The reaction mixture was stirred for another 15 minutes and ~5 g of solid NH₄Cl were added. Ammonia was allowed to evaporate and the residue was diluted with water. Extraction with ethyl acetate, washing with brine and removal of solvent afforded a viscous liquid which was distilled at 165°C/1 Torr to furnish pure diol 13 (6.9 g) in 45% yield. IR (neat): νmax 3406, 3061, 1440, 1273 cm⁻¹; 1H NMR (200 MHz, CDCl₃): δ 4.00–4.30 (m, 2H), 3.59 (s, 3H), 3.54 (s, 3H), 3.42–3.31 (m, 1H), 3.06 (dd, 1H, J = 9.5, 4.3), 2.4 (br s, 2H), 1.89 (dd, 1H, J = 12.8, 8.8, 5), 1.68–1.50 (m, 1H); 13C NMR (50 MHz, CDCl₃): δ 130.1, 129.4, 114.8, 76.4, 74.8, 72.9, 38.9 (2C), 52.5, 51.6, 51.4, 30.6; m/z (EI): 328 (M⁺ – Cl); Found: C, 39.55; H, 3.81. C₂₅H₂₆O₄Cl₂ requires: C, 39.9; H, 3.88%.

5,5-Dimethyl-4,6-dioxatricyclo[8.2.1.0²,⁶,⁰,¹²]tridec-11-en-13-one 14
To a solution of diol 13 (8 g, 35.4 mmol) in acetone (25 ml), Amberlyst-15 catalyst was added and the resulting heterogeneous mixture was stirred at rt for 6 h. Filtration of the resin and concentration furnished the keto-acetonide 14 (6.1 g) in 83% yield as a colorless solid. Mp: 74°C; IR (KBr): νmax 1778, 1373, 1062, 719 cm⁻¹; 1H NMR (200 MHz, CDCl₃): δ 0.54–0.51 (m, 2H), 4.39 (m, 1H), 1.47 (m, 1H), 3.10–3.20 (m, 1H), 2.20–2.00 (m, 1H), 1.60–1.55 (m, 1H), 1.47 (s, 3H), 1.26 (s, 3H); 13C NMR (50 MHz, CDCl₃): δ 202.2, 133.0, 132.0, 110.8, 84.3, 83.4, 52.0, 48.5, 42.2, 35.0, 27.9, 25.4; m/z (EI): 207 (M⁺ – 1); Found: C, 70.62; H, 7.34. C₂₅H₂₆O₄ requires: C, 70.89; H, 7.32%.

Methyl 4-hydroxy-2,2-dimethyl-3b,4,5,7a,8,8a-hexahydro-3aH-indeno[1,2-d][1,3]dioxole-7-carboxylate 15 and methyl 7-hydroxy-2,2-dimethyl-3b,6,7,7a,8,8a-hexahydro-3aH-indeno[1,2-d][1,3]dioxole-4-carboxylate 16
To an ice-cooled solution of the tricyclic ketone 14 (4.4 g, 20 mmol) and anhydrous Na₂CO₃ (2.2 g, 20.6 mmol in dry dichloromethane (50 ml) m-chloroperoxybenzoic acid (5.4 g, 70%, 22 mmol) was added and the reaction mixture was stirred for 30 min. The reaction was quenched with saturated aq. NaHCO₃ and the contents were stirred for another 15 min. The organic layer was separated and the aqueous layer was further extracted with dichloromethane. The combined organic extracts were again washed with saturated aq. NaHCO₃ followed by brine.

The crude mixture of the lactones (~4.8 g) obtained after the removal of solvent was dissolved in dry methanol (15 ml) and a small pellet of KOH was added. The contents were then stirred for 20 min at room temperature. After the removal of the methanol under vacuum, the residue was diluted with water and extracted with diethyl ether. The etheral layer was washed with water and dried. The crude residue obtained after the removal of the solvent was loaded on the silica gel column and eluted with 20% ethyl acetate–hexane to furnish the hydroxy esters 15 (1.85 g) and 16 (1.62 g) in 63% overall yield in 55:45 ratio.

Methyl 4-hydroxy-2,2-dimethyl-3b,4,5,7a,8,8a-hexahydro-3aH-indeno[1,2-d][1,3]dioxole-7-carboxylate 17
A mixture of 15 (1.5 g, 5.6 mmol), methyl iodide (2.6 ml, 40 mmol) and KOH (~360 mg, 6 mmol) was stirred at rt for 2 h and then loaded on a pad of silica gel and eluted with 10% EtOAc–hexane to afford 17 (1.41 g) in 90% yield. IR: νmax 1712, 1649, 1437, 1379, 1248, 750 cm⁻¹; 1H NMR (200 MHz, CDCl₃): δ 6.87 (m, 1H), 4.87 (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), 1.49 (s, 1H), 1.35 (m, 1H), 1.30 (s, 3H); 13C NMR (50 MHz, CDCl₃): δ 167.1, 136.4, 129.3, 109.8, 84.7, 70.0, 65.3, 51.7, 42.6, 41.0, 34.5, 30.3, 26.4, 24.1; m/z (EI): 253 (M⁺ – 15).

Methyl 4-hydroxy-2,2-dimethyl-3b,4,5,7a,8,8a-hexahydro-3aH-indeno[1,2-d][1,3]dioxole-7-carboxylate 18
To an ice-cooled solution of 17 (1.2 g, 4.25 mmol) in benzene (15 ml) was added Celite (200 mg), PDC (3.16 g, 8.5 mmol) and 0.4 ml of 80% tert-butyl hydroperoxide. The reaction mixture was stirred at rt for 1 h and then filtered through a small Celite pad. The crude product obtained after evaporation of the solvent was loaded on a silica gel column and eluted with 10% EtOAc–hexane to furnish enone 18 (230 mg) and unreacted starting material (450 mg) in 30% yield (on the basis of recovery of starting material). IR: νmax 1702, 1701, 1439, 1325, 1209, 756 cm⁻¹; 1H NMR (200 MHz, CDCl₃): δ 6.71 (s, 1H), 4.86 (t, 1H, J = 5.4), 4.69 (d, 1H, J = 5.6), 3.85 (s, 3H), 3.61 (s, 3H), 3.59–3.50 (m, 2H), 2.70–2.48 (m, 2H), 1.85–1.75 (m, 1H), 1.49 (s, 3H), 1.33 (s, 3H); 13C NMR (50 MHz, CDCl₃): δ 198.5, 165.9, 148.2, 131.7, 109.7, 82.2, 80.5, 78.6, 59.5, 52.7, 51.4, 37.7, 37.3, 26.2, 23.8; m/z (EI): 296 (M⁺ + 1); Found: C, 60.62; H, 6.83. C₂₅H₂₆O₄ requires: C, 60.80; H, 6.80%.

Methyl 5-hydroxy-4-methoxy-2,2-dimethyl-3b,4,5,7a,8,8a-hexahydro-3aH-indeno[1,2-d][1,3]dioxole-7-carboxylate 19
To a solution of enone 18 (220 mg, 0.74 mmol) and CeCl₃·7H₂O (335 mg, 0.9 mmol) in dry methanol (5 ml) was added NaBH₄ (35 mg, 0.9 mmol) at ~20°C and the mixture was stirred for 15 min at the same temperature. Methanol was removed under reduced pressure and the residue obtained was

dissolved in water and extracted with ethyl acetate. The organic extract was washed, dried and evaporated to furnish aliphatic alcohol 19 (130 mg) in 62% yield. IR: νmax 3460, 1715, 1440, 1335, 755 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.25 (s, 3H), 1.46 (s, 3H), 1.55–1.72 (m, 1H), 2.07 (s, 3H), 2.10 (m, 1H), 2.90 (t, 1H, J = 5.6), 4.61 (d, 1H, J = 5.6), 7.65–7.68 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 13.5, 26.7, 49.0, 108.1, 127.1, 29.2, 30.9, 37.5, 40.9, 45.0, 58.9, 61.4, 67.9, 76.1, 105.7, 113.4, 115.4, 115.9, 121.0, 132.7, 134.8, 134.9, 137.2, 137.3, 140.6, 145.8, 150.2, 150.8, 158.8, 158.9, 161.4, 164.0, 164.2, 164.3, 170.4, 170.5, 170.7.

Acknowledgements

We thank Professor B. Fraser-Reid for providing the spectral data on 24 for comparison purposes. D. S. thanks UGC, New Delhi, for a research fellowship. This research was supported by the Jawaharlal Nehru Center for Advanced Scientific Research, Bangalore.

References


Some portions of this work have been reported previously, see: G. Mehta and D. S. Reddy, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2125.

