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Asymmetric Synthesis of Sceletium Alkaloids: (–)-Mesembrine, (+)-Sceletium A-4, (+)-Tortuosamine and (+)-*N*-Formyltortuosamine

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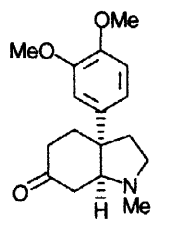
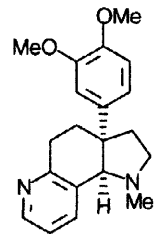
Abstract: Three procedures for the transformation of achiral 1-(3,4-dimethoxyphenyl)-cyclohexene into enantiomerically pure 2-(3,4-dimethoxyphenyl)cyclohex-2-en-1-ol have been established at first. Utilizing the (–)-cyclohexenol thus obtained, the four titled Sceletium alkaloids have been synthesized in the natural enantiomeric forms.

Keywords: Alkaloids; Asymmetric synthesis; Coupling reactions; Palladium and compounds; Pyridines

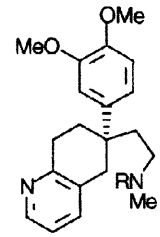
Recently, we established[1] the absolute structures of (+)-sceletium A-4 **2**, (+)-tortuosamine **3a** and (+)-*N*-formyltortuosamine **3b**, the Sceletium alkaloids isolated more than three decades ago,[2] by correlation to (–)-mesembrine **1**, another member of the Sceletium group, whose absolute structure was known.[3] We report here a new asymmetric route to these four natural products starting from an achiral starting material (**Fig 1**).



(–)-mesembrine **1**



(+)-sceletium A-4 **2**



(+)-tortuosamine **3a** : R=H
(+)-*N*-formyltortuosamine **3b** : R=CHO

Fig. 1

Treatment of 1-(3,4–dimethoxyphenyl)cyclohexene[4] **4**, obtained in 88% overall yield from cyclohexanone, with *m*-chloroperbenzoic acid (*m*CPBA) afforded in one-step the tertiary ester (±)-**5** which rearranged to the secondary ester (±)-**6**, mp 135.5–137 °C, on exposure to a diluted base. Dehydration of (±)-**6** followed by

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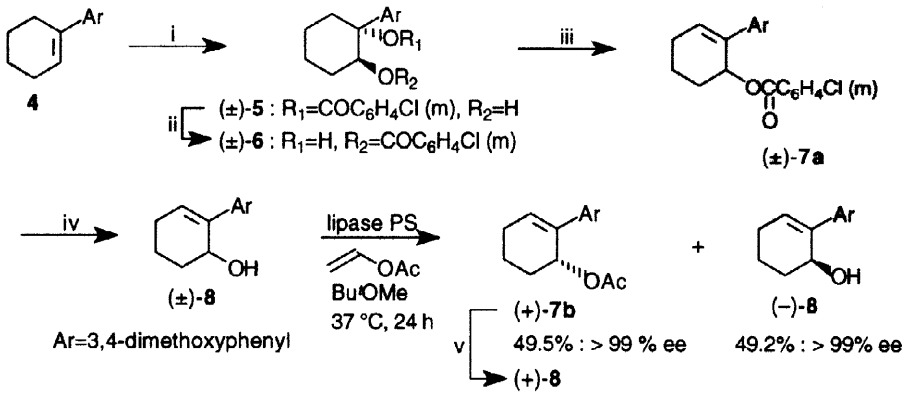
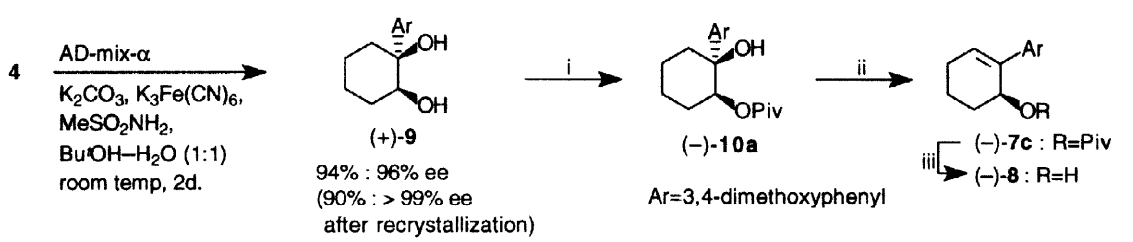
methanolysis of the resulting (±)-**7a** gave allyl alcohol (±)-**8**, mp 78–79 °C. When (±)-**8** was stirred with vinyl acetate in *tert*-butyl methyl ether in the presence of lipase PS[5] (*Pseudomonas cepacia*, Amano), clear-cut enantiospecific transesterification occurred to give (+)-acetate (+)-**7b** (> 99 % ee)[6], mp 43–45 °C, $[\alpha]_D^{29}$ +178.8 (*c* 1.0, $CHCl_3$), leaving (–)-alcohol (–)-**8** (> 99 ee)[6], mp 78–79.5 °C, $[\alpha]_D^{29}$ –107.8 (*c* 1.1, $CHCl_3$), the former of which gave (+)-**8**, mp 78–79.5 °C, $[\alpha]_D^{25}$ +106.1 (*c* 1.0, $CHCl_3$), on methanolysis (**Scheme 1**).



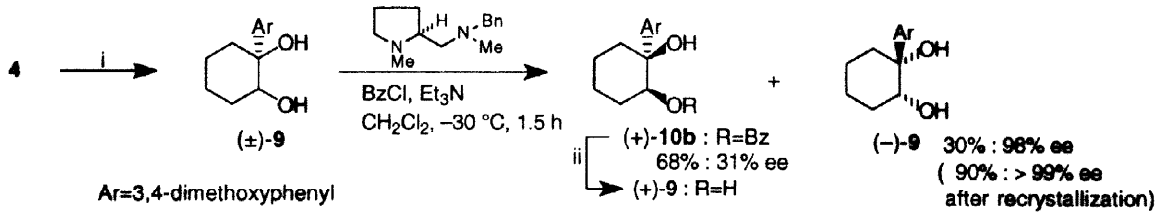
Scheme 1: *Reagents and conditions*: i, *m*CPBA, $NaHCO_3$ CH_2Cl_2, 0 °C, 15 min (85%); ii, 0.5 N NaOH (cat.), THF, rt., 10 min (81%); iii, $POCl_3$, pyridine, 50 °C, 48 h (82%); iv, K_2CO_3, MeOH, rt., 24 h (91%); v, K_2CO_3, MeOH, rt., 12 h (98%).

On the other hand, **4** was dihydroxylated in the presence of AD-mix-α[7] to give *cis*-diol (+)-**9** in 96% ee[6] which gave pure (+)-**9**, mp 123–124.5 °C, $[\alpha]_D^{31}$ +5.1 (*c* 1.0, $CHCl_3$), on single recrystallization. (–)-**9** was also obtained in 98% ee in the presence of an AD-mix-β reagent.[7] Monoacylation of (+)-**9** followed by treatment of the resulting pivalate (–)-**10a**, mp 143–144 °C, $[\alpha]_D^{30}$ –27.1 (*c* 1.1, $CHCl_3$), with the Burgess reagent[8] afforded (–)-**7c**, $[\alpha]_D^{27}$ –120.5 (*c* 1.4, $CHCl_3$), which was reduced with lithium aluminum hydride (LAH) to give cyclohexenol (–)-**8**, mp 78–79 °C, $[\alpha]_D^{28}$ –105.4 (*c* 1.1, $CHCl_3$) (**Scheme 2**).



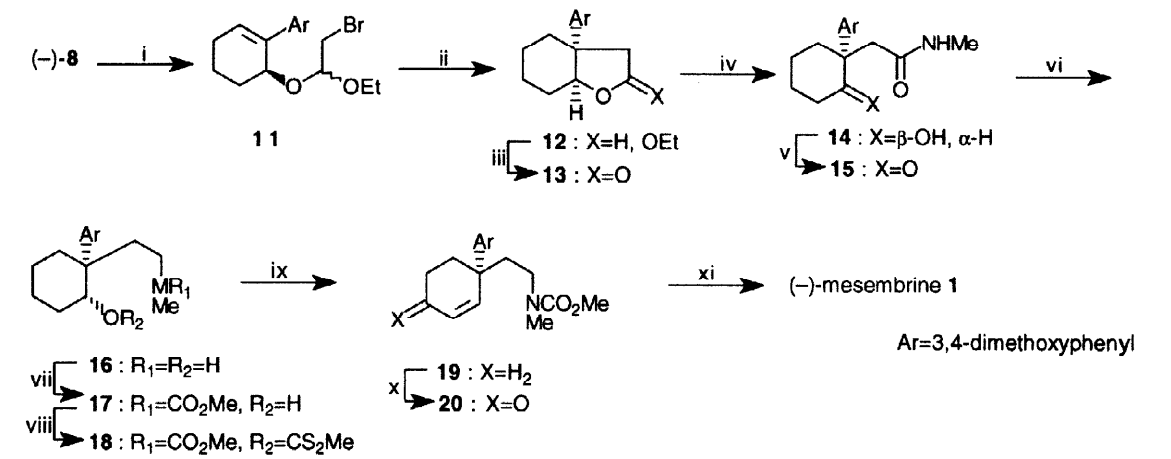
Scheme 2: *Reagents and conditions*: i, PivCl, Et_3N, DMAP (cat.), CH_2Cl_2, rt., 24 h (96%); ii, $Et_3NSO_2NCO_2Me$, toluene, 50 °C, 1 h (98%); iii, $LiAlH_4$, THF, rt., 2 h (98%).

In the third procedure, *cis*-diol (±)-**9**, mp 97–99 °C, prepared from **4**, was treated with benzoyl chloride in the presence of (*S*)-2-(*N*-benzyl,*N*-methyl)aminomethyl-1-methylproline[9] to give *mono*-benzoate (+)-**10b** (31% ee)[6] leaving (–)-**9** (98% ee),[6] the latter of which gave pure (–)-**9**, mp 123–124.5 °C, $[\alpha]_D^{29}$ –4.9 (*c* 1.0, $CHCl_3$), on recrystallization (**Scheme 3**).



Scheme 3: *Reagents and conditions*: i, OsO_4 (cat.), NMO, rt., 2 h (96%); ii, 2*N* NaOH-MeOH (1:4), rt., 4 h, (98%).

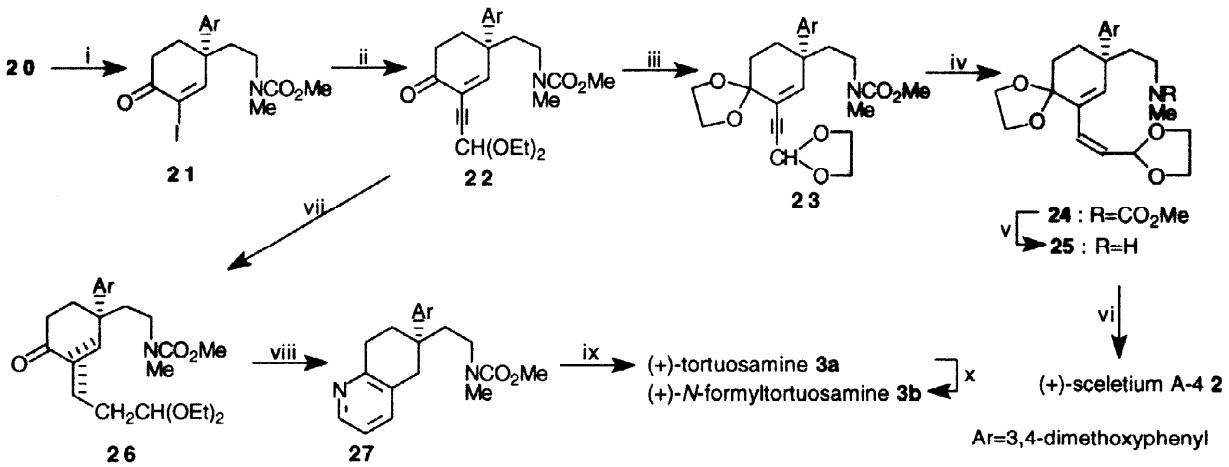
Having established three routes to enantiomerically pure **8**, (–)-**8** was treated with ethyl vinyl ether in the presence of NBS[10] to give bromo-acetal **11**. Radical cyclization[11] occurred by treating **11** with sodium borohydride in the presence of a catalytic amount of tributylstannyl chloride and AIBN[12,13] in *tert*-butanol to give **12** which, on reaction with *m*CPBA in the presence of boron trifluoride etherate,[14] afforded γ-lactone **13**, $[\alpha]_D^{25}$ –31.3 (*c* 1.0, $CHCl_3$). To introduce the cyclohexene double bond, **13** was first converted[15] to keto-amide **15**, $[\alpha]_D^{28}$ +161.8 (*c* 1.1, $CHCl_3$), *via* **14**, $[\alpha]_D^{29}$ –36.6 (*c* 1.1, $CHCl_3$). Reduction of **15** with LAH afforded single amino-alcohol[16] **16** which was transformed into cyclohexene **19**, $[\alpha]_D^{27}$ –30.9 (*c* 1.1, $CHCl_3$), through **17**, $[\alpha]_D^{27}$ –42.8 (*c* 1.2, $CHCl_3$), and **18**, $[\alpha]_D^{27}$ +67.1 (*c* 1.08, $CHCl_3$). Allylic oxidation[17] of **19** gave cyclohexenone **20**, $[\alpha]_D^{27}$ –34.4 (*c* 0.7, $CHCl_3$), which was decarbamoylated to give (–)-mesembrine **1**, $[\alpha]_D^{28}$ –57.0 (*c* 1.3, MeOH) [lit.[18]: $[\alpha]_D$ –62.8 (*c* 1.40, MeOH)], by concurrent cyclization[19] (**Scheme 4**).



Scheme 4: *Reagents and conditions*: i, ethyl vinyl ether, NBS, Et_2O, 0 °C ~ rt., 24 h (98%); ii, Bu_3SnCl (cat.), AIBN (cat.), $NaBH_4$, Bu'OH, reflux, 6 h (87%); iii, *m*CPBA, $BF_3{\cdot}OEt_2$ (cat.), CH_2Cl_2, rt., 1 h (93%); iv, Me_2NH_2Cl, Me_3Al, THF, reflux, 8 h (98%); v, Swern oxid. (80%); vi, $LiAlH_4$, THF, reflux, 2d; vii, $ClCO_2Me$, Et_3N, CH_2Cl_2, rt., (75% from **15**); viii, CS_2, NaH, MeI, THF, rt., 6 h (91%); ix, *o*-dichlorobenzene, reflux, 18 h (82%); x, CrO_3-3,5-dimethylpyrazole, CH_2Cl_2, –15 °C, 2 h (73%); xi, 10% KOH, EtOH, reflux, 24 h (35%).

To synthesize the three other Sceletium alkaloids, **20** was treated with iodine in carbon tetrachloride containing pyridine[1,20] to afford α-iodo-enone **21**, $[\alpha]_D^{29}$ +42.4 (*c* 1.0, $CHCl_3$), which, on the palladium-mediated coupling[1,21] with propynal diethyl acetal in the presence of diisopropylamine,[22] gave enyne **22**, $[\alpha]_D^{27}$ +39.0 (*c* 1.2, $CHCl_3$). To carry out partial reduction of the acetylene functionality, **22** was transformed first into *bis*-acetal **23**, $[\alpha]_D^{27}$ +19.0 (*c* 0.4, $CHCl_3$), which afforded single diene **24**, $[\alpha]_D^{27}$ –11.7 (*c* 1.2, $CHCl_3$), on hydrogenation on Lindlar catalyst. Alkaline hydrolysis of **24** gave amine **25** which was heated with ammonium acetate in acetic acid to furnish (+)-sceletium A-4 **2**, mp 154.5–155.5 °C, $[\alpha]_D^{28}$ +130.5 (*c* 1.0, MeOH) [lit.: mp 153.5–154.5 °C, $[\alpha]_D$ +131 (MeOH)[2b]; mp 153.5–154.5 °C, $[\alpha]_D^{27}$ +120.5 (*c* 1.10, MeOH)[1]], by concurrent deacetalization and pyridine ring formation.

On the other hand, direct hydrogenation of **22** on Lindlar catalyst brought about acetylene hydrogenation and olefin migration to afford diene mixture **26** which was heated with ammonium acetate in acetic acid to give pyridine **27**, $[\alpha]_D^{30}$ +107.0 (*c* 0.6, $CHCl_3$). On alkaline hydrolysis, **27** gave (+)-tortuosamine[2e] **3a**, $[\alpha]_D^{27}$ +157.9 (*c* 0.5, MeOH) which afforded (+)-*N*-formyltortuosamine **3b**, $[\alpha]_D^{27}$ +133.3(*c* 0.5, MeOH), $[\theta]_{282}$ +13290, $[\theta]_{266}$ −7596 (95% EtOH) [lit.[2e]: $[\theta]_{282}$ +12000, $[\theta]_{266}$ −6380 (95% EtOH)], on exposure to acetic formic anhydride[2e] (**Scheme 5**).



Scheme 5: *Reagents and conditions*: i, I_2, pyridine, CCl_4, rt., 20 h (88%); ii, propynal diethyl acetal, $PdCl_2(PPh_3)_2$ (cat.), CuI (cat.), Pr^i_2NH, THF, 0 °C, 40 min (95%); iii, ethylene glycol, *p*TsOH (cat.), benzene, reflux, 12 h (76%); iv, H_2, Lindlar cat., AcOEt. rt., 2.5 h (97%); v, 50% KOH-EtOH (1:2), reflux, 24 h; vi, NH_4OAc, 80% AcOH, 100 °C, 24 h (82% from **24**); vii, H_2, Lindlar cat., AcOEt, rt., 3 h (98%); viii, NH_4OAc, AcOH, 100 °C, 24 h (76%); ix, 50% KOH-EtOH (1:2), reflux, 36 h (94%); x, AcOCHO, 0 °C, 6 h (91%)

References and Notes

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