First enantiocontrolled synthesis of sceletium alkaloid A-4: determination of the absolute configuration

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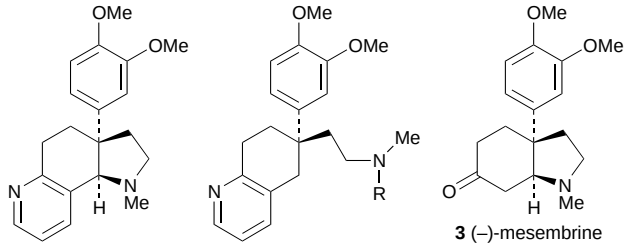
Sceletium A-4, a pyridine alkaloid isolated from the *Sceletium* species, has been synthesized for the first time in an enantiocontrolled manner along with (−)-mesembrine, an alkaloid isolated from the same plant, starting from a chiral cyclohexadienone synthon to determine the absolute configuration.

The alkaloid (+)-sceletium A-4[1,2] **1** is a minor constituent of various *Sceletium* species of the family *Aizonaceae* and was



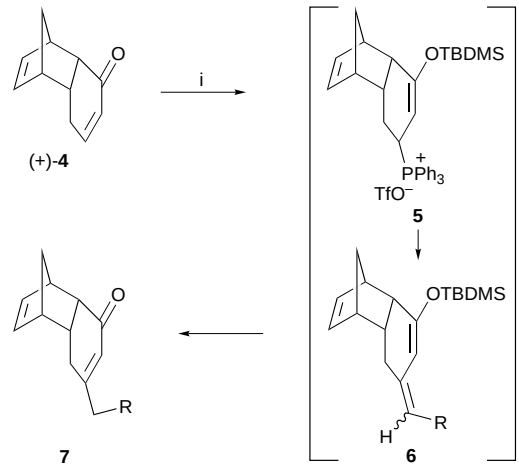
isolated with congeners such as (−)-tortuosamine[2b,d] **2a**, (−)-*N*-formyltortuosamine[2d] **2b** and (−)-mesembrine[1] **3**. (+)-Sceletium A-4 **1** afforded (−)-tortuosamine **2a** on hydrogenolysis[2b,d] while the latter afforded (−)-*N*-formyltortuosamine **2b** on formylation, indicating that they possess the same absolute configuration at the benzylic quaternary centers. The structure determination, both by a single-crystal X-ray analysis[2c] and by racemic syntheses,[3] revealed that (+)-sceletium A-4 **1** possesses the same relative stereochemistry as (−)-mesembrine **3** with respect to two stereogenic centers. However, the absolute configuration of the former alkaloid has not been correlated to the latter, whose absolute configuration has been determined both by X-ray analysis[4] and by enantioselective syntheses.[5]

In order to determine the absolute configuration of (+)-sceletium A-4 **1** as well as of the two congeners **2** by correlation to the stereochemistry of (−)-mesembrine **3**, we examined enantiocontrolled synthesis of Sceletium A-4 **1** along with (−)-mesembrine **3** using the common tricyclic chiral building block (+)-**4**, serving as a chiral cyclohexadienone.[6,7] We report here the first enantiocontrolled synthesis of (+)-sceletium A-4 **1** and a new synthesis of (−)-mesembrine **3** leading to the unambiguous determination of the absolute configuration of (+)-sceletium A-4 **1** and its two congeners, (−)-tortuosamine **2a** and (−)-*N*-formyltortuosamine **2b**.

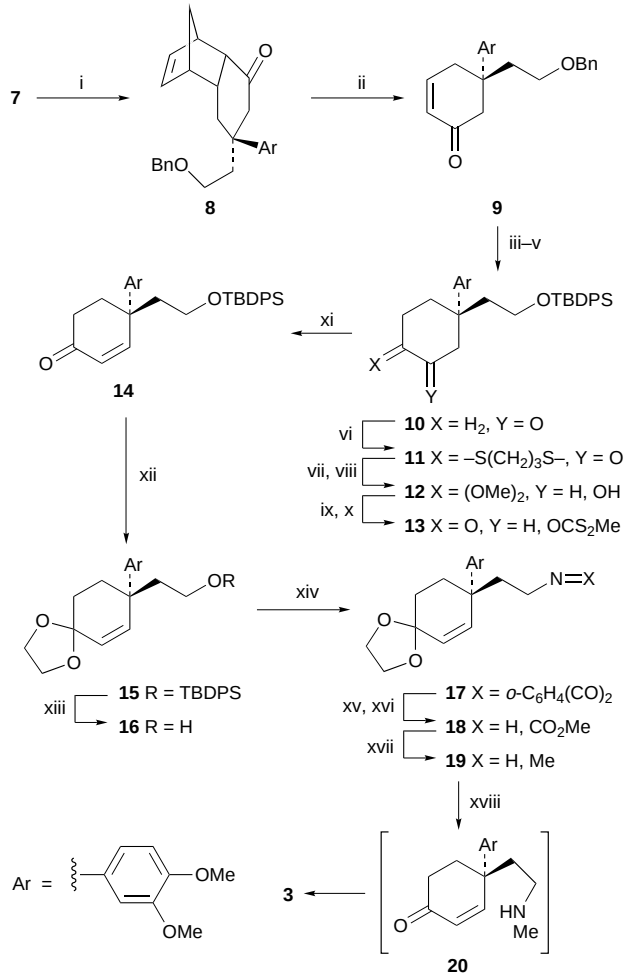
We have recently demonstrated[8] that the tricyclic enone **4** may be β-alkylated to furnish the β-substituted enone **7** by a single-flask sequential Michael–Wittig process[9] *via* the phosphonium trifrate **5** and the 1,3-diene **6** (Scheme 1). Employing this procedure, we prepared the β-substituted enone‡ **7** (R = CH_2OBn), $[\alpha]_D^{28}$ +164.3 (*c* 1.13, $CHCl_3$), in 71% yield from (+)-**4** and 2-benzyloxyacetaldehyde. Reaction of **7** with 3,4-dimethoxyphenylmagnesium bromide in the presence of copper(I) bromide–dimethyl sulfide complex[10] proceeded from the convex face to give the β,β-disubstituted ketone **8** after acid workup, which on thermolysis afforded the cyclohexenone **9**, $[\alpha]_D^{28}$ +64.2 (*c* 1.38, $CHCl_3$). To transpose its 5,5-disubstituted cyclohex-2-enone structure to the 4,4-disubstituted cyclohex-2-enone structure **14**, **9** was first transformed into the α-diketone monothioketal **11** *via* the cyclohexanone **10**, by sequential 1,4-reduction,[11] debenzylation, silylation and α,α-thioketalization.[12] On reduction of the ketone functionality, followed by the thioketal–methyl ketal exchange reaction,[13] **11** furnished the secondary alcohol **12** which was then transformed to the methyl xanthate **13** after acid hydrolysis. Finally, **13** was heated to give the 4,4-disubstituted cyclohex-2-enone **14**, $[\alpha]_D^{29}$ −21.7 (*c* 0.62, $CHCl_3$).

To produce (−)-mesembrine **3**, **14** was first transformed into the ketal alcohol **16** *via* **15**. Employing the Mitsunobu reaction,[14] **16** was next converted to the secondary amine **19**, *via* the imide **17**, and the carbamate **18**. Finally, **18** was treated with perchloric acid in THF to give (−)-mesembrine **3**, $[\alpha]_D^{29}$ −55.4 (*c* 1.16, MeOH) [lit.,[5b] $[\alpha]_D^{30}$ −57.5 (*c* 0.146, MeOH) (Scheme 2).

Having obtained (−)-mesembrine **3**, we investigated the transformation of the same enone **14** into (+)-sceletium A-4 **1** to correlate the stereochemistry (Scheme 3). The enenone **14** was exposed to I_2 in CH_2Cl_2 containing pyridine[15] to furnish the α-iodo ketone **21**. Palladium-mediated cross-coupling reaction[16] between the iodo ketone **21** and *N*-*tert*-butylcarbamoylprop-1-yne yielded the enyne **22** which was converted into the ketal **24** *via* **23** by sequential ketalization and desilylation. Employing a five-step sequence including the Mitsunobu reaction,[14] **24** was transformed into the bis-carbamate **27** *via* the imide enyne **25** and the imide diene **26**. On standing in diluted hydrochloric acid in THF at room temperature, **27** collapsed gradually to the pyridine **30** through a concurrent deketalization, chemoselective decarbamoylation, double cyclization and dehydrogenation, presumably through the allyl amine **28** and the dihydropyridine **29**. The pyridine **30** was exposed to TFA to give the secondary amine **31**, which was immediately subjected



Scheme 1 *Reagents and conditions*: i, PPh_3, TBDMSOTf, THF, −78 °C, then Bu^nLi, −78 °C, then RCHO, 10% HCl



Scheme 2 *Reagents and conditions*: i, 3,4-$(MeO)_2C_6H_3MgBr$, $CuBr{\cdot}SMe_2$, Me_3SiCl, HMPA, THF; ii, Ph_2O, *ca.* 260 °C (77% from **7**); iii, DIBAL-H, CuI, HMPA, THF; iv, H_2, 10% Pd–C; v, Bu^tPh_2SiCl, imidazole, DMF (72% from **9**); vi, $TsS(CH_2)_3STs$, Bu^tOK, THF–Bu^tOH (70%); vii, $NaBH_4$, $CeCl_3{\cdot}7H_2O$; viii, $(CF_3CO_2)IPh$, MeOH (87% from **11**); ix, NaH, CS_2, MeI, THF; x, 70% $HClO_4$–THF (1 : 20); xi, *o*-$C_6H_4Cl_2$, *ca.* 180 °C (77% from **12**); xii, $(CH_2OH)_2$, TsOH, C_6H_6, (100%); xiii, Bu_4NF, THF (94%); xiv, phthalimide, PPh_3, $Pr^iO_2CN{=}NCO_2Pr^i$ (DIPAD), THF (94%); xv, hydrazine·H_2O, EtOH, reflux; xvi, $ClCO_2Me$, Et_3N, CH_2Cl_2 (79% from **17**); xvii, $LiAlH_4$, THF, reflux; xviii, aq. $HClO_4$, THF (66% from **18**)

to the Eschweiler–Clarke reaction[17] to afford (+)-Sceletium A-4 **1**, mp 153.5–154.5 °C, $[\alpha]_D^{27}$ + 120.5 (*c* 1.10, MeOH) (lit.,[2a] mp 153.5–154.5; lit.,[2b] 132–134 °C, lit.,[2c] $[\alpha]_D$ +131 (MeOH); lit.,[2d] $[\alpha]_D$ +131 (EtOH)). The synthetic material had a circular dichroism (CD) spectrum (in 95% EtOH) showing the first cotton effect (positive) at 278 nm, the second (positive) at 274 nm and the third (negative) at 247 nm which was identical to that reported[2d] for (+)-sceletium A-4 **1** (positive at 278 nm, positive at 274 nm and negative at 247 nm in 95% EtOH). Since (+)-**1** thus obtained has the same CD spectrum as the natural product, the absolute configuration of natural (+)-Sceletium A-4 **1** as well as its two natural congeners, (+)-tortuosamine **2a** and (−)-*N*-formyltortuosamine **2b**, has now been established as that shown by correlation to (−)-mesembrine **3**.

Notes and References

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‡ Satisfactory analytical (high resolution mass) and spectral (IR, ^1H NMR and mass) data were obtained for all new isolable compounds.

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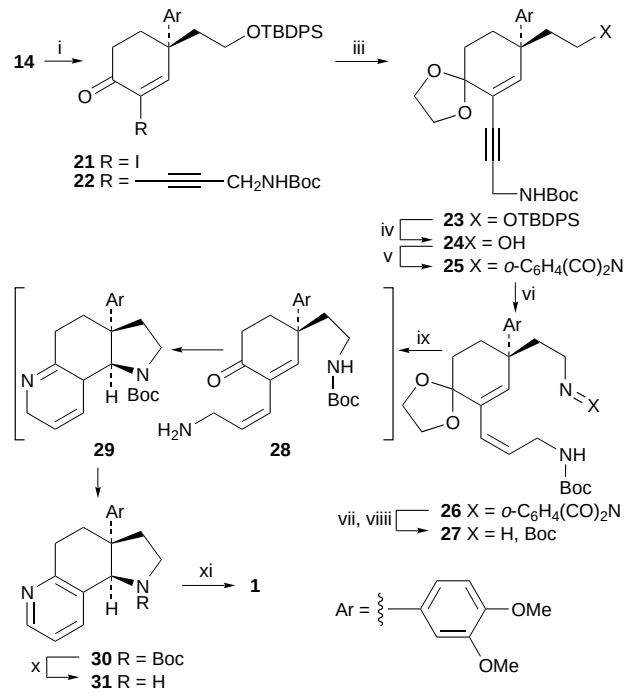

Scheme 3 *Reagents and conditions*: i, I_2, Py, CH_2Cl_2 (97%); ii, $HC{\equiv}CCH_2NHBoc$, $PdCl_2(PPh_3)_2$ (cat), CuI, Et_3N (91%); iii, $(CH_2OH)_2$, TsOH, C_6H_6 (71%); iv, Bu_4NF, THF (100%); v, phthalimide, PPh_3, DIPAD, THF (90%); vi, H_2, Lindlar catalyst, MeOH (86%); vii, hydrazine·H_2O, EtOH, reflux; viii, Boc_2O, Et_3N, CH_2Cl_2 (85% from **26**); ix, 10% HCl–THF (1 : 4) (42%); x, TFA, $CHCl_3$; xi, 35% HCHO, HCO_2H (67%)

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Received in Cambridge, UK, 23rd December 1997; 7/09212A