

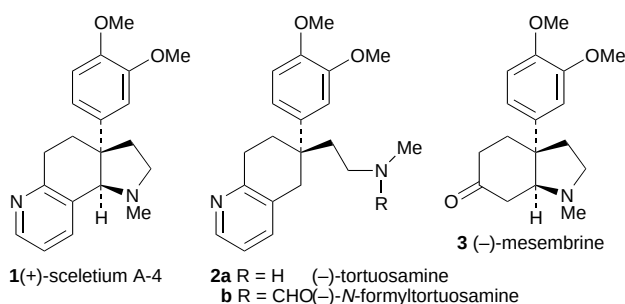
First enantiocontrolled synthesis of sceletium alkaloid A-4: determination of the absolute configuration

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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 *Aizoonaceae* and was



isolated with congeners such as (–)-tortuosamine^{2b,d} **2a**, (–)-*N*-formyltortuosamine^{2d} **2b** and (–)-mesembrine¹ **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 analysis⁴ and by enantioselective syntheses.⁵

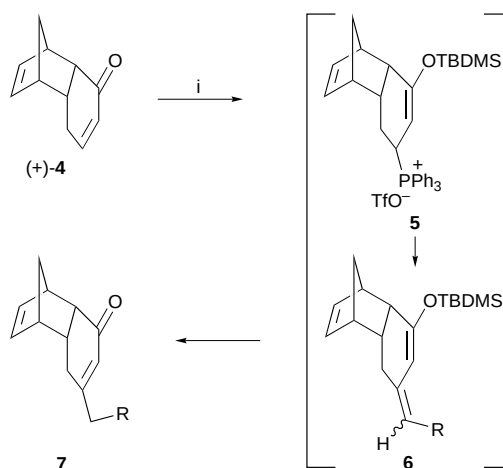
In order to determine the absolute configuration of (+)-sceletium A-4 **1** as well as of the two congeners **2** by correlation to the stereochemistry of (–)-mesembrine **3**, we examined enantiocontrolled synthesis of Sceletium A-4 **1** along with (–)-mesembrine **3** using the common tricyclic chiral 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 demonstrated⁸ that the tricyclic enone **4** may be β -alkylated to furnish the β -substituted enone **7** by a single-flask sequential Michael–Wittig process⁹ via the phosphonium triflate **5** and the 1,3-diene **6** (Scheme 1). Employing this procedure, we prepared the β -substituted enone† **7** (R = CH₂OBn), [α]_D²⁸ +164.3 (c 1.13, CHCl₃), 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 complex¹⁰ proceeded from the convex face to give the β,β -disubstituted ketone **8** after acid

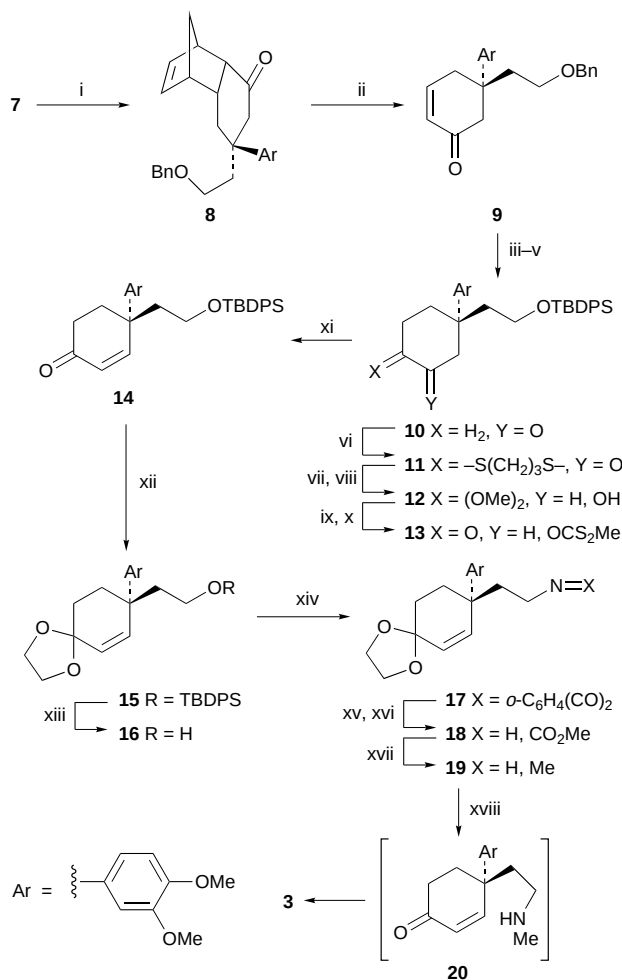
workup, which on thermolysis afforded the cyclohexenone **9**, [α]_D²⁸ +64.2 (c 1.38, CHCl₃). To transpose its 5,5-disubstituted cyclohex-2-enone structure to the 4,4-disubstituted cyclohex-2-enone structure **14**, **9** was first transformed into the α -diketone monothioacetal **11** via the cyclohexanone **10**, by sequential 1,4-reduction,¹¹ debenzoylation, silylation and α,α -thioacetalization.¹² On reduction of the ketone functionality, followed by the thioacetal–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**, [α]_D²⁹ –21.7 (c 0.62, CHCl₃).

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**, [α]_D²⁹ –55.4 (c 1.16, MeOH) [lit.,^{5b} [α]_D³⁰ –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 enone **14** was exposed to I₂ in CH₂Cl₂ containing pyridine¹⁵ to furnish the α -iodo ketone **21**. Palladium-mediated cross-coupling reaction¹⁶ between the iodo ketone **21** and *N*-*tert*-butylcarbamoyl-prop-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, PPh₃, TBDMSOTf, THF, –78 °C, then BuⁿLi, –78 °C, then RCHO, 10% HCl



Scheme 2 Reagents and conditions: i, 3,4-(MeO)₂C₆H₃MgBr, CuBr·SMe₂, Me₃SiCl, HMPA, THF; ii, Ph₂O, ca. 260 °C (77% from 7); iii, DIBAL-H, CuI, HMPA, THF; iv, H₂, 10% Pd-C; v, Bu^tPh₂SiCl, imidazole, DMF (72% from 9); vi, TsS(CH₂)₃STs, Bu^tOK, THF-Bu^tOH (70%); vii, NaBH₄, CeCl₃·7H₂O; viii, (CF₃CO₂)IPh, MeOH (87% from 11); ix, NaH, CS₂, MeI, THF; x, 70% HClO₄-THF (1:20); xi, o-C₆H₄Cl₂, ca. 180 °C (77% from 12); xii, (CH₂OH)₂, TsOH, C₆H₆, (100%); xiii, Bu₄NF, THF (94%); xiv, phthalimide, PPh₃, Pr^tO₂CN=NCO₂Pr^t (DIPAD), THF (94%); xv, hydrazine·H₂O, EtOH, reflux; xvi, ClCO₂Me, Et₃N, CH₂Cl₂ (79% from 17); xvii, LiAlH₄, THF, reflux; xviii, aq. HClO₄, THF (66% from 18)

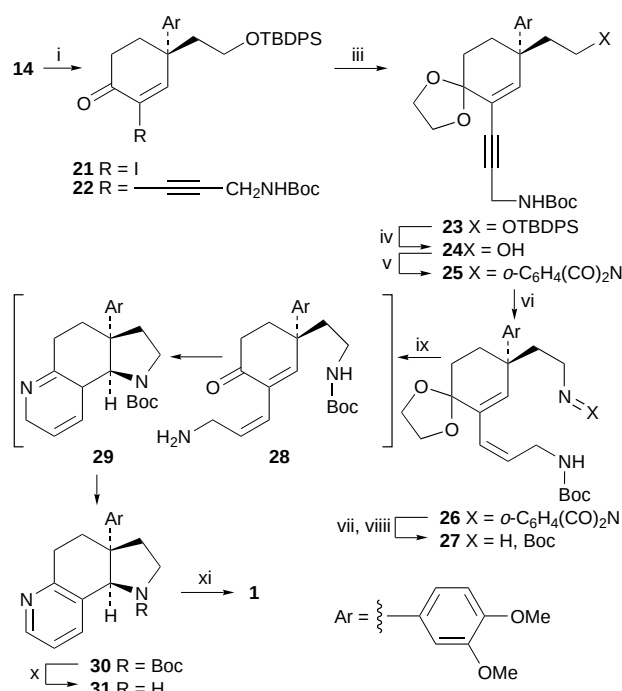
to the Escheiwer–Clarke reaction¹⁷ to afford (+)-Sceletium A-4 **1**, mp 153.5–154.5 °C, [α]_D²⁷ +120.5 (c 1.10, MeOH) (lit.,^{2a} mp 153.5–154.5; lit.,^{2b} 132–134 °C, lit.,^{2c} [α]_D +131 (MeOH); lit.,^{2d} [α]_D +131 (EtOH)). The synthetic material had a circular dichroism (CD) spectrum (in 95% 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, I₂, Py, CH₂Cl₂ (97%); ii, HC≡CCH₂NHBoc, PdCl₂(PPh₃)₂ (cat), CuI, Et₃N (91%); iii, (CH₂OH)₂, TsOH, C₆H₆ (71%); iv, Bu₄NF, THF (100%); v, phthalimide, PPh₃, DIPAD, THF (90%); vi, H₂, Lindlar catalyst, MeOH (86%); vii, hydrazine·H₂O, EtOH, reflux; viii, Boc₂O, Et₃N, CH₂Cl₂ (85% from 26); ix, 10% HCl-THF (1:4) (42%); x, TFA, CHCl₃; xi, 35% HCHO, HCO₂H (67%)

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