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A new enantioselective route to the *Sceletium* alkaloids via a cyclopentanone–cyclohexenone transformation

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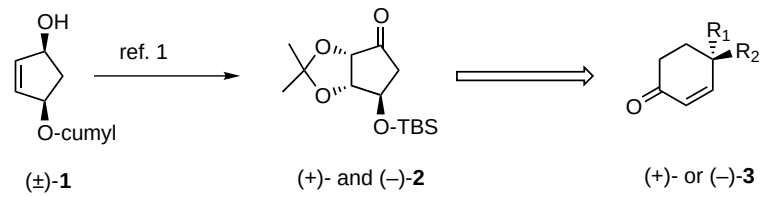
Abstract—An enantioselective route to the *Sceletium* alkaloids has been developed using the 2,3,4-trioxycyclopentanone chiral building block by carrying out its conversion into a 4,4-disubstituted cyclohexenone derivative. © 2002 Elsevier Science Ltd. All rights reserved.

We have developed an efficient method for the preparation of the 2,3,4-trioxygenated cyclopentanone **2** having a dioxabicyclo[3.3.0]heptane framework in both enantiomeric forms by employing a lipase-mediated kinetic resolution of racemic *cis*-4-cumyloxycyclopentenol (±)-**1** as the key step.[1] Because of its functionality and sterically biased framework, the enantiopure cyclopentanone **2** has already been used as a convenient chiral building block allowing facile diastereocontrol[1,2] in the enantio- and diastereocontrolled synthesis of several natural products. We have been trying for some time to develop the enantio- and diastereocontrolled construction of less accessible 4,4-disubstituted cyclohexenones **3** which possess versatile synthetic utility.[3] Accordingly, we attempted the conversion of the readily accessible enantiopure cyclopentanone **2** into enantiopure 4,4-disubstituted cyclohexenones **3**. We wish to report here the successful construction of the enantiopure 4,4-disubstituted cyclohexenone (*R*)-(−)-**4** leading to four of the *Sceletium* alkaloids,[4] synthesized earlier by our group from chiral cyclohexanoid precursors[5,6] (Scheme 1).

Since preparation of the key cyclohexene (*R*)-(−)-**4**, in the previous syntheses, involved somewhat cumbersome steps, we hope to develop a more facile enantioselective route to this compound from the chiral cyclopentanone (−)-**2**, thereby, demonstrating its increased synthetic potential and a more convenient enantioselective route to the *Sceletium* alkaloids (Scheme 2).

The synthesis began with the reaction of the cyclopentanone (−)-**2** and 3,4-dimethoxyphenyllithium, prepared in situ from 3,4-dimethoxyphenyl bromide with butyllithium, to give the benzylic *endo*-alcohol **5**. The reaction proceeded diastereoselectively to furnish the benzylic tertiary alcohol **5** as a single product. The product **5** obtained was desilylated with tetrabutylammonium fluoride (TBAF) to afford the diol **6**, $[\alpha]_D^{27}$ +27.5 (*c* 0.5, $CHCl_3$). Oxidation of the diol **6** with pyridinium chlorochromate (PCC) afforded the hydroxy-ketone **7**. Upon stirring in warm acetic acid,[1] the hydroxy-ketone **7** furnished the cyclopentenone **8**, $[\alpha]_D^{30}$ +112.2 (*c* 2.4, $CHCl_3$), through a β-elimination of the tertiary hydroxyl functionality with the acetonide functionality intact. Owing to the sterically biased structure, the enone **8** allowed diastereoselective reduction of the ketone functionality with sodium borohy-



(±)-**1** (+)- and (−)-**2** (+)- or (−)-**3**

Scheme 1.

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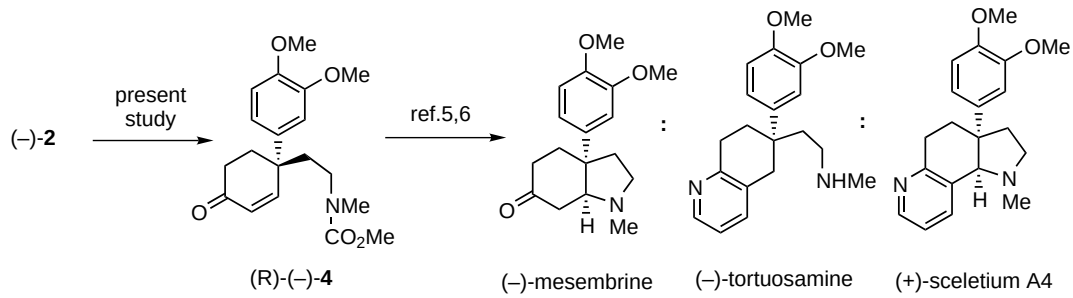
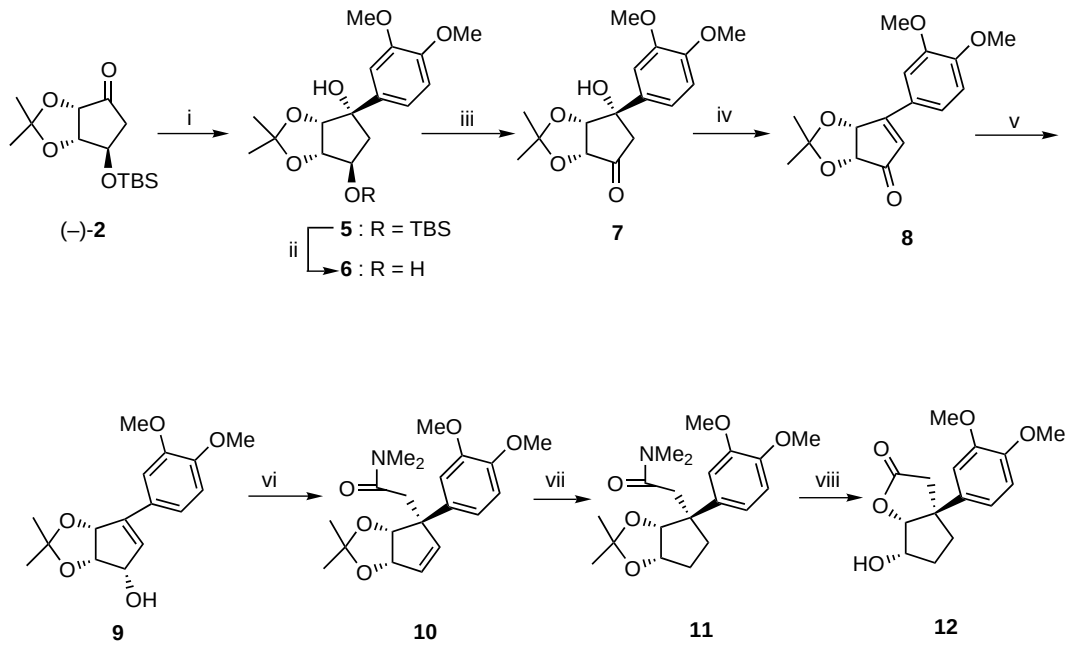


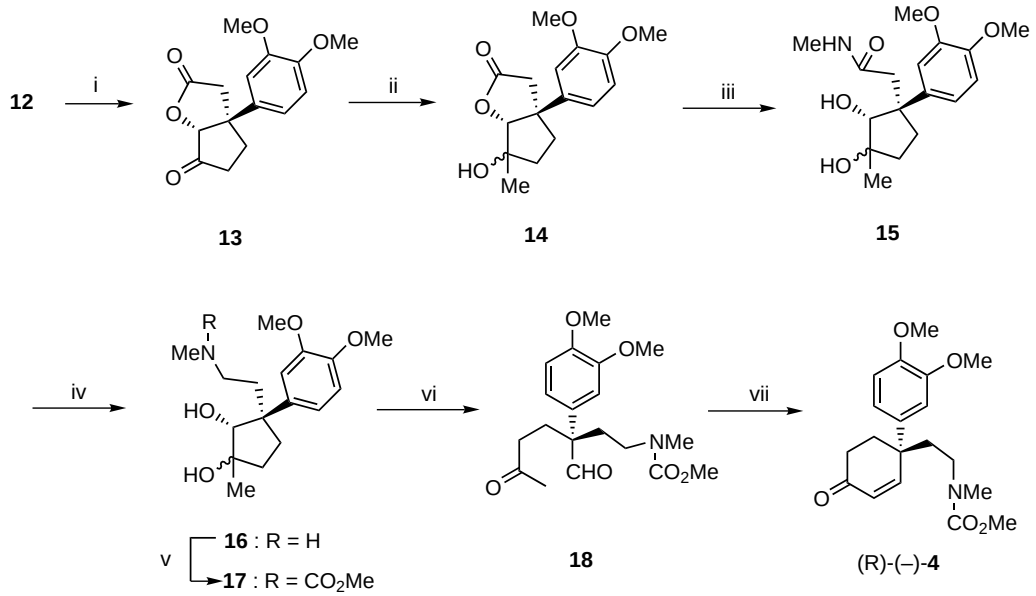
Scheme 2.

dride in the presence of cerium(III) chloride[7] to give the single cyclopentenol **9**, $[\alpha]_D^{27}$ +75.4 (*c* 2.4, $CHCl_3$), having the all-*cis* oxygen stereochemistry, which is essential for the next transformation. Thus, the Eschenmoser reaction[8] of the cyclopentenol **9** with dimethylacetamide dimethyl acetal in decalin at 220°C afforded the single cyclopentene **10**, $[\alpha]_D^{25}$ +52.1 (*c* 1.0, $CHCl_3$), which was hydrogenated to give the cyclopentane **11** having the acetic acid moiety *cis* to the acetonide moiety. Due to the stereochemistry of the cyclopentane ring, the amide **11** allowed consecutive facile deacetonization and lactonization under acidic methanolysis conditions to give the δ-hydroxy-γ-lactone **12**, $[\alpha]_D^{30}$ +10.4 (*c* 0.7, $CHCl_3$), as a single product. The overall yield of the hydroxy-lactone **12** from the chiral cyclopentenol (–)-**2b** was 39% in eight steps (Scheme 3).

After the neighboring two *cis*-secondary oxygen functionalities that originated from the starting material (–)-**2** had been discriminated by regioselective lactone formation, the remaining secondary hydroxy functionality of the γ-lactone **12** was oxidized under Dess–Martin conditions[9] to give the keto-lactone **13**, $[\alpha]_D^{31}$ +20.8 (*c* 2.0, $CHCl_3$), in good yield. Reaction of the keto-lactone **13** with the complex generated in situ from methyllithium and cerium (III) chloride[10] in THF at –20°C allowed chemoselective reaction at the ketone carbonyl center to yield the hydroxy-lactone **14** as a mixture of two epimers with the lactone functionality intact. It was also found that the same mixture **14** could also be obtained in a comparable yield in THF in the absence of the cerium salt at –78°C. The hydroxy-lactone **14** obtained was then exposed to the complex generated in situ from methylamine hydrochloride and trimethylaluminum[11] in THF at reflux to give the dihydroxy-amide mixture **15**. On sequential reduction with lithium aluminum hydride and *N*-carbomethoxylation with methyl chlorocarbonate, the amide **15** furnished the carbamate **17** via the secondary amine **16**. At this stage, the 1,2-glycol functionality of the carbamate **17** was cleaved with sodium periodate in aqueous THF to give the keto-aldehyde **18**. Upon stirring in aqueous



Scheme 3. *Reagents and conditions*: (i) 6-bromo-3,4-dimethoxybenzene, butyllithium, THF, –78°C, (80%). (ii) TBAF, THF (94%). (iii) PCC, NaOAc. (iv) AcOH, 40°C (81%, two steps). (v) $NaBH_4$, $CeCl_3$–$7H_2O$, MeOH, –20°C (98%). (vi) $MeCNMe_2(OMe)_2$, decalin, reflux (76%). (vii) H_2, 10% Pd–C, AcOEt. (viii) *p*-TsOH (cat.), MeOH, reflux (85%, two steps).



Scheme 4. *Reagents and conditions*: (i) Dess–Martin periodinane, CH_2Cl_2 (88%). (ii) MeLi, $CeCl_3$, THF or MeLi, THF, –78°C. (iii) $MeNH_3Cl$, Me_3Al, THF, reflux (62%, two steps). (iv) $LiAlH_4$, dioxane, reflux. (v) $ClCO_2Me$, Hünig base, CH_2Cl_2 (73%, two steps). (vi) $NaIO_4$, THF–H_2O (1:1). (vii) 10% KOH–MeOH (1:5) (49%, two steps).

methanol containing potassium hydroxide,[12] the keto-aldehyde **18** furnished, via a consecutive intramolecular aldol reaction and dehydration, the cyclohexenone (*R*)-(−)-**4**, $[\alpha]_D^{27}$ −34.2 (*c* 0.4, $CHCl_3$) {Ref. 6: $[\alpha]_D^{27}$ −34.4 (*c* 0.4, $CHCl_3$)}, which was used as the key intermediate in the synthesis of the *Sceletium* alkaloids. The overall yield of the key intermediate (*R*)-(−)-**4** from the hydroxy-lactone **12** was 20% in seven steps. Thus, a new route to the key 4,4-disubstituted cyclohexenone intermediate (*R*)-(−)-**4** has been developed using the readily accessible cyclopentane chiral building block (+)-**2**. From the intermediate (*R*)-(−)-**4**, the *Sceletium* alkaloids were obtained: (−)-mesembrine in one step,[6] (−)-tortuosamine in five steps,[6] and (+)-sceletium A4 in six steps.[6] Although it took 15 steps to convert the starting chiral cyclopentane (+)-**2** into the key cyclohexenone (*R*)-(−)-**4**, the present synthesis may be more easily carried out than the two previous ones since no intractable reagents or difficult conditions are involved. The present procedure may also be applicable to the synthesis of the morphine alkaloids since we also have developed[13] the enantio- and diastereo-selective route to morphinanone derivatives via the 4,4-disubstituted cyclohexenone intermediate closely related to **4** (Scheme 4).

In conclusion, we have demonstrated a transformation of the chiral cyclopentane chiral building block into a chiral 4,4-disubstituted cyclohexenone used as the key intermediate of the *Sceletium* alkaloids using a cyclopentanone–cyclohexenone transformation pathway. We have, thus, extended the utility of the cyclopentane that we obtained as a chiral building block.

Acknowledgements

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