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Enantiospecific Construction of Quaternary Carbon Center via Intramolecular 1,3-Dipolar Cycloaddition. A New Route to Natural (–)-Mesembrine from (*S*)-*O*-Benzylglycidol

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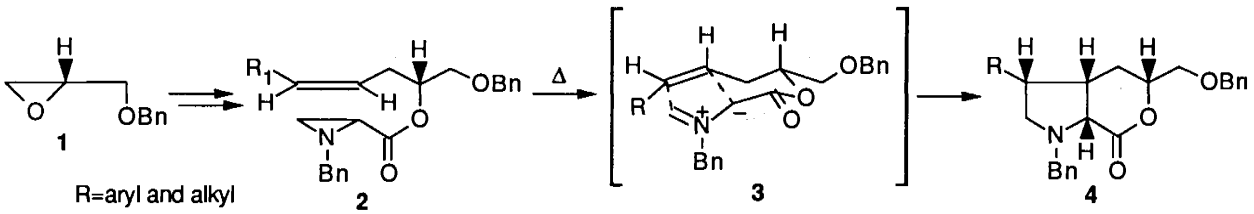
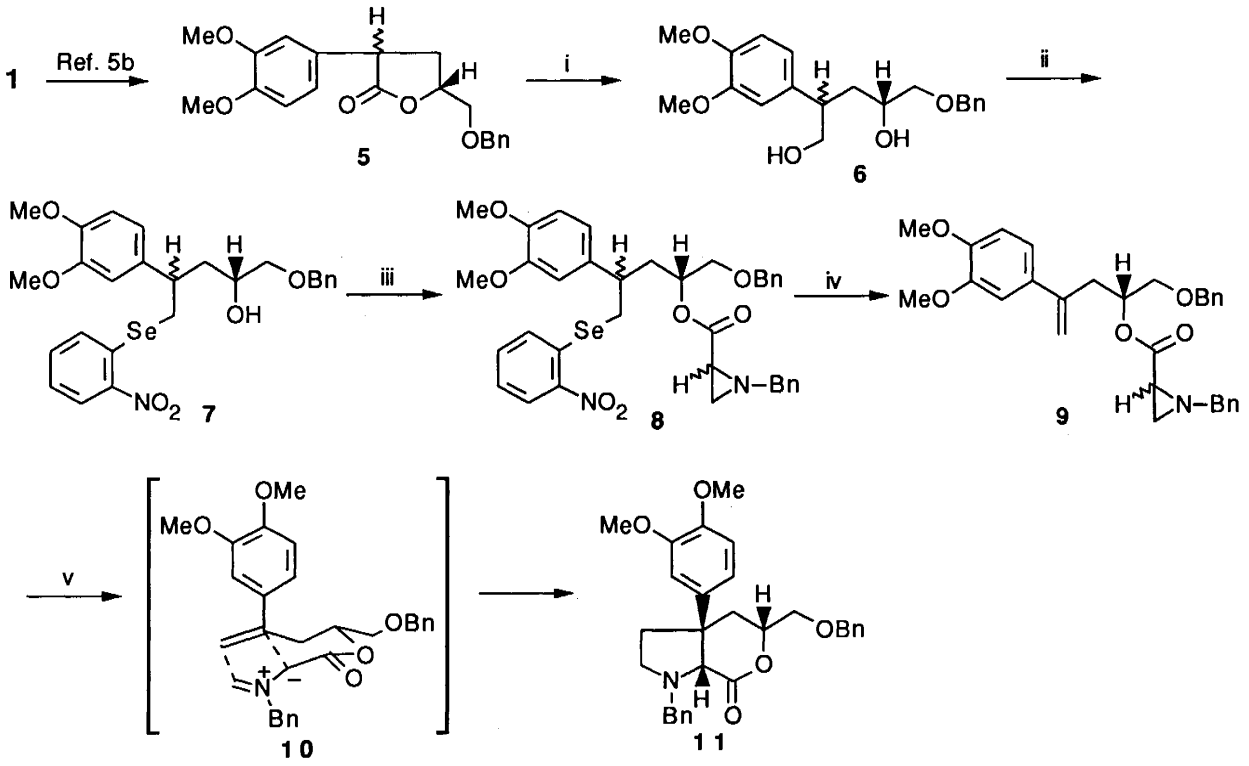
Thermolysis of the aziridine ester, obtained from (*S*)-*O*-benzylglycidol, afforded the pyrrolidine lactone bearing a quaternary carbon center stereo-specifically in a good yield via intramolecular cycloaddition of the 1,3-dipole. The adduct (**11**) could be converted into natural (–)-mesembrine, the major alkaloid of *Sceletium namaquense*, and its *N*-demethyl derivative via a 8 step sequence of reactions.

Recently, we disclosed an efficient enantiocontrolled synthesis of the kainoid amino acids[1] starting from (*S*)-*O*-benzylglycidol[2,3] (**1**) employing intramolecular 1,3-dipolar cycloaddition reaction[4] as the key step. In the key stage, a transient azomethine ylide (**3**) generated from an aziridine ester (**2**) was postulated to adopt the conformation placing the bulky benzyloxymethyl group in an equatorial disposition which resulted in stereoselective formation of three new chiral tertiary carbon centers on the pyrrolidine (**4**) (Scheme 1). We report herein an extention of the method for the construction of a quaternary carbon center which led to a new synthesis of (–)-mesembrine[5] (**19**), the major alkaloid of *Sceletium namaquense*,[6] and its *N*-demethyl derivative (**29**), a potential key intermediate of a number of the Amaryllidaceae alkaloids.[7]



Scheme 1.

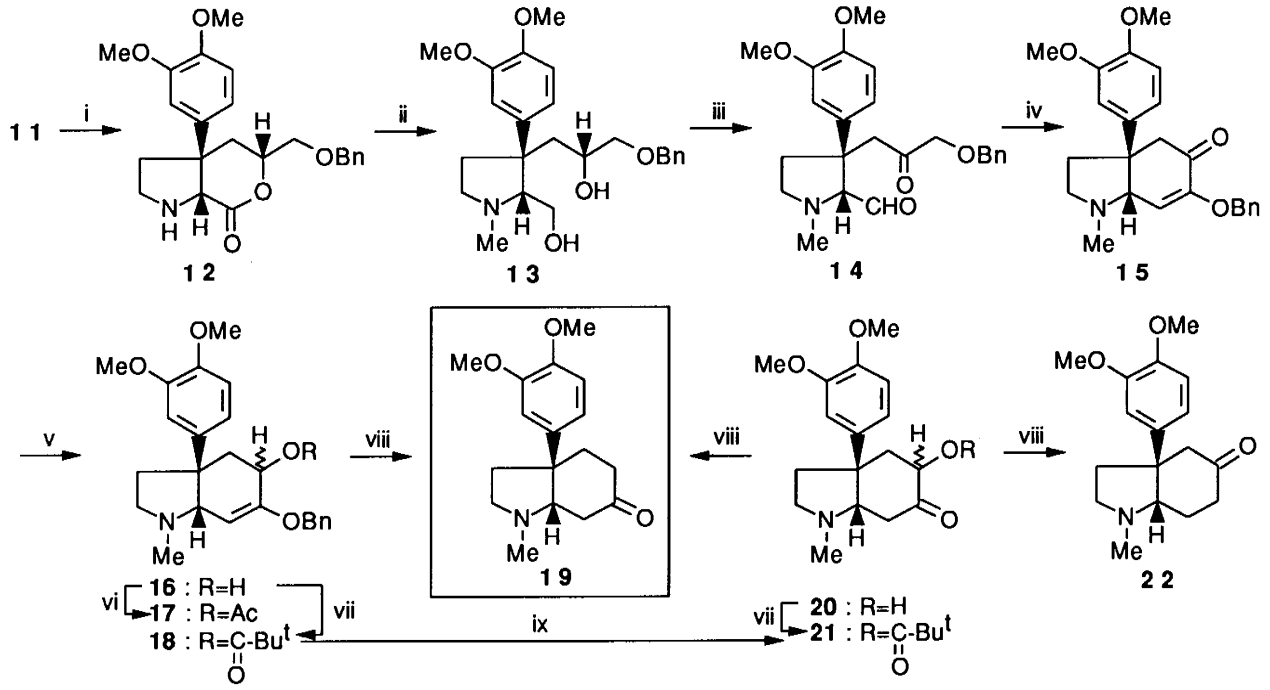
Reduction of the known γ-lactone[5b] (**5**), obtained as a diastereomeric mixture from (*S*)-*O*-benzylglycidol (**1**) in 2 steps in 65% overall yield, was reduced to the diol (**6**), in 97% yield, of which primary hydroxy group could be selectively replaced under the Grieco conditions,[8] to give the selenide (**7**) in 94% yield. On treatment with 2,3-dibromopropionyl chloride in the presence of triethylamine followed by benzylamine in the same flask,[4] **7** afforded the aziridine ester (**8**), in 93% yield which was converted into the 1,1-disubstituted olefin (**9**), quantitatively, with exposure to 30% hydrogen peroxide.[8] When **9** was heated at 250 °C in degased xylene using a sealed tube, the expected reaction occurred within 20 min to furnish the pyrrolidine lactone (**11**), $[\alpha]_D^{27}$ +78.3° (*c* 2.79, $CHCl_3$), bearing a quaternary carbon center in 85% yield as a single isomer. Although the actual structure could not be determined at this stage, later conversion revealed that the product possessed the stereochemistry shown which may be formed via the 1,3-dipole adopting the conformation (**10**) placing the benzyloxymethyl group in an equatorial disposition as similar in the *Z*-olefins[1] (Scheme 2).



Scheme 2.

Conditions: i) $LiAlH_4$, THF, 0 °C, 40 min; ii) *o*-$NO_2C_6H_4SeCN$, $^nBu_3P$, THF, rt, 1h; iii) 2,3-dibromopropionyl chloride, Et_3N, CH_2Cl_2, −10 °C, 30 min then benzylamine, rt, 5 h; iv) 30% H_2O_2, CH_2Cl_2, 0 °C – rt, 9 h; v) sealed tube, xylene, 250 °C, 20 min.

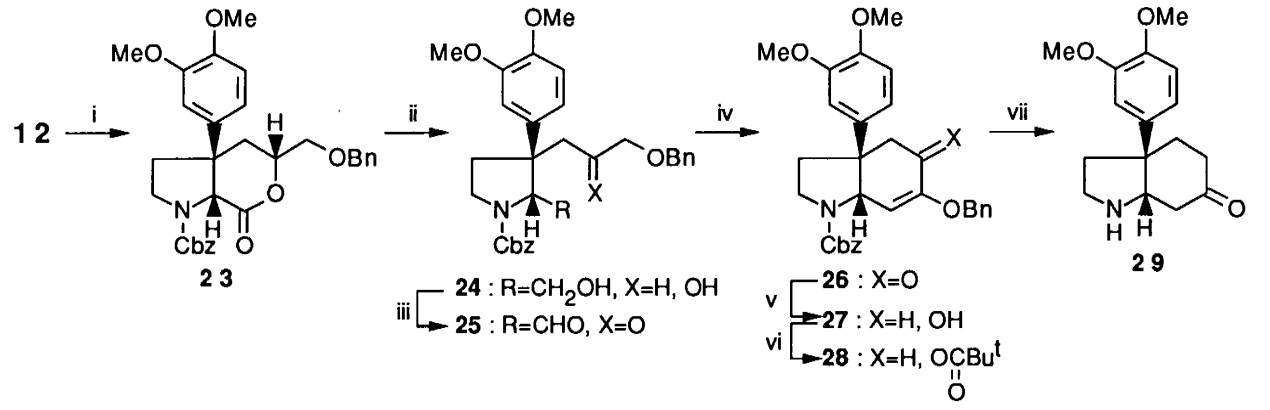
Fortunately, it was found that catalytic hydrogenolysis of **11** occurred chemoselectively without affecting the *O*-benzyl group to give the secondary amine (**12**), $[\alpha]_D^{27}$ −8.7° (*c* 0.71, $CHCl_3$), in 88% yield when palladium hydroxide on carbon (20%) was used as catalyst.[9] Treatment of **12** with 37% formalin and sodium borohydride brought about spontaneous reductive *N*-methylation and reduction of the lactone group to afford the aminodiol (**13**), $[\alpha]_D^{31}$ −20.8° (*c* 0.74, $CHCl_3$), in 70% yield. Oxidation of **13** under the Swern conditions[10] followed by intramolecular aldolization of the resulting keto-aldehyde (**14**) furnished the enone (**15**), mp 164 °C, $[\alpha]_D^{31}$ −9.4° (*c* 0.61, $CHCl_3$), in 75% overall yield. Reduction of **15** under the Luche conditions[11] yielded the allylic alcohol (**16**), as a mixture which was acylated to give the acetate (**17**) and the pivalate (**18**) in 76 and 47% overall yield, respectively. When the acetate (**17**) was treated with lithium in liquid ammonia, concurrent debenzylation and reductive elimination occurred to furnish (−)-mesembrine (**19**) in 27% yield accompanied by the acyloin (**20**) in 25% yield latter of which was resulted by competing deacylation under the conditions. Since the pivalate (**18**) gave a similar result under the same conditions, **18** was first acid hydrolyzed to give the α-keto ester (**21**), in 49% yield, which then was treated under the Birch conditions to furnish (−)-mesembrine (**19**) in 58% yield without forming the acyloin (**20**). (−)-Mesembrine (**19**) thus obtained was identical in all respects with an authentic material[5b] and showed virtually the same rotation values [$[\alpha]_D^{30}$ −57.5° (*c* 0.15, MeOH)] [lit.: $[\alpha]_D$ −55.4° (MeOH)[12]; −62.8° (*c* 1.40, MeOH)[5b]]. The by-product acyloin (**20**) was found to be very labile under acylation conditions and it gave a mixture of four regio- and stereo-isomers of the pivalates [(**21**) and its regio-isomers], in 88% yield, which on Birch reduction gave rise to 22% of (−)-mesembrine (**19**) and 26% of (−)-isomesembrine (**22**), $[\alpha]_D^{30}$ −38.7° (*c* 0.5, $CHCl_3$) (Scheme 3).



Scheme 3.

Conditions: i) H_2, 20% $Pd(OH)_2$-C, MeOH, rt, 8 h; ii) 37% formalin, MeOH, 0 °C, 1 h then $NaBH_4$, 0 °C – rt; iii) oxalyl chloride, DMSO, CH_2Cl_2, –71 °C, 1.5 h then Et_3N, –71 °C – rt; iv) 0.5N NaOH, EtOH, rt, 11 h; v) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 1.5 h; vi) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C – rt, 9 h; vii) Me_3CCOCl, Et_3N, DMAP (cat.), CH_2Cl_2, rt, 12 h; viii) Li, liq. NH_3, –33 °C, 10 min; ix) 6N HCl-EtOH (1:2), 60 °C, 2 h.

On the other hand, the secondary amine (**12**) was transformed to the carbamate (**23**), $[\alpha]_D^{25}$ –34.8° (*c* 1.07, $CHCl_3$), in 85% yield, which gave the diol (**24**), $[\alpha]_D^{27}$ –70.8° (*c* 1.38, $CHCl_3$), in 81% yield on reduction with sodium borohydride. Upon sequential Swern oxidation and aldolization **24** afforded the enone (**26**), $[\alpha]_D^{30}$ +84.8° (*c* 0.96, $CHCl_3$), via **25** in 63% overall yield. **26** was then transformed into the pivalate mixture (**28**) in 78% overall yield via the alcohol (**27**). Birch reduction of **28** afforded *N*-demethyl-mesembrine (**29**) in 53% yield as a single product by concurrent decarbamoylation, debenzylation, and reductive elimination without formation of an acyloin by-product. Although **29** has been neither found naturally nor obtained synthetically so far, it may be potentially useful as a key intermediate for the chiral construction of a considerable number of the Amaryllidaceae alkaloids[7] (Scheme 4).



Scheme 4.

Conditions: i) BnOCOCl, Et_3N, CH_2Cl_2, 0 °C, 40 min; ii) $NaBH_4$, aq. EtOH (30%), rt, 9 h; iii) oxalyl chloride, DMSO, CH_2Cl_2, –70 °C, 1.5 h then Et_3N, 20 min; iv) 0.5N NaOH, EtOH, 0 °C, 12 h; v) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 30 min; vi) Me_3CCOCl, Et_3N, DMAP (cat.), CH_2Cl_2, 12 h; vii) Li, liq. NH_3, –33 °C, 5 min.

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13) Spectroscopic data for the representative compounds; **11**: IR(film): n 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$): d 1.90 (1H, dd, *J*=1.8, 14.0 Hz), 2.08 (1H, ddd, *J*=12.2, 9.8, 5.5 Hz), 2.16 (1H, ddd, *J*=12.8, 7.9, 5.5 Hz), 2.48 (1H, t, *J*=12.8 Hz), 2.50 (1H, dd, *J*=15.9, 10.4 Hz), 3.11 (1H, ddd, *J*=8.5, 8.5, 5.5 Hz), 3.54 (1H, d, *J*=13.4 Hz), 3.57 (1H, s), 3.59 (1H, dd, *J*=11.0, 4.9 Hz), 3.62 (1H, dd, *J*=11.0, 4.9 Hz), 3.85 (3H, s), 3.87 (3H, s), 4.16-4.19 (1H, m), 4.47 (1H, d, *J*=13.4 Hz), 4.55 (1H, d, *J*=12.0 Hz), 4.59 (1H, d, *J*=12.0 Hz), 6.68 (1H, d, *J*=7.3 Hz), 6.69 (1H, s), 6.79 (1H, d, *J*=8.6 Hz), 7.22-7.35 (10H, m). **15**: Ir (Nujol): n 1690, 1630 cm^{-1}; ^{1}H-nmr ($CDCl_3$): d 1.95-1.27 (2H, m), 2.36 (3H, s), 2.48-2.79 (2H, m), 2.88 (1H, d, *J*=15.6 Hz), 3.31 (1H, d, *J*=15.6 Hz), 3.13 (1H, d, *J*=5.4 Hz), 3.83 (3H, s), 3.84 (3H, s), 5.68 (1H, d, *J*=5.9 Hz), 6.75 (3H, s), 7.31 (5H, s). **22**: Ir (film): n 1705 cm^{-1}; ^{1}H-nmr ($CDCl_3$): d 1.70-2.70 (8H, m), 2.39 (3H, s), 2.79 (2H, s), 3.30 (1H, td, *J*=8.8, 2.9 Hz), 3.86 (3H, s), 3.88 (3H, s), 6.83-6.85 (3H, m). **26**: Ir (film): n 1705, 1690, 1630 cm^{-1}; ^{1}H-nmr ($CDCl_3$): d 2.14 (1H, d, *J*=5.7 Hz), 2.22 (1H, d, *J*=7.1 Hz), 2.95 (2H, d, *J*=10.5 Hz), 3.20-3.55 (2H, m), 3.79 (3H, s), 3.86 (3H, s), 4.75 (0.8H, s), 4.90 (1.2H, s), 5.02 (0.4H, d, *J*=4.2 Hz), 5.17 (2H, s), 5.19 (0.6H, d, *J*=4.3 Hz), 5.81 (0.4H, d, *J*=4.2 Hz), 6.10 (0.6H, d, *J*=4.2 Hz), 6.77-6.89 (3H, m), 7.35-7.46 (10H, m). **29**: IR (film): n 3400, 1710 cm^{-1}; ^{1}H-nmr ($CDCl_3$): d 2.0-2.3 (7H, m), 2.62 (2H, dd, *J*=5.7, 4.6 Hz), 2.95-3.25 (2H, m), 3.89 (3H, s), 3.90 (3H, s), 5.60 (1H, br.s), 6.80-6.94 (3H, m).

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