Tetrahedron Letters 51 (2010) 2354–2355

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective formal synthesis of (−)-mesembrane by intramolecular condensation of chiral amide and 1,3-cyclohexanedione moiety

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ARTICLE INFO

Article history:
Received 30 January 2010
Revised 18 February 2010
Accepted 23 February 2010
Available online 1 March 2010

ABSTRACT

A new stereoselective formal synthesis of (−)-mesembrane has been achieved by intramolecular condensation of chiral amide and 1,3-cyclohexanedione moiety. The precursor amide was readily prepared by condensation of the corresponding chiral amine and acid. Condensation provided moderate ratios of ene-amide derivatives and the following transformation of functional groups has yielded the known precursor for (−)-mesembrane, resulting in formal synthesis.

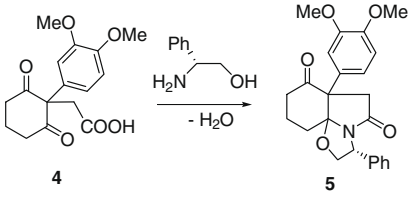
Mesembrane **1** is a member of the *Sceletium* alkaloids,[1] which has the basic structural element of *cis*-3*a*-aryloctahydroindole skeleton **3**. Crinine **2** is also a prototype of the alkaloids.[2] These alkaloids containing quaternary center at C_{3a} constitute a large family of products that have attracted considerable attention over the years due to their diverse and interesting structures,[3] and several asymmetric approaches have also been suggested (Fig. 1).[4]

Initially, as a new effort toward the asymmetric synthesis of mesembrane, we tried to apply desymmetrization of enantiotopic 1,3-dicarbonyl groups of compound **4**[5] by condensation with chiral phenylglycinol (Scheme 1).[7]

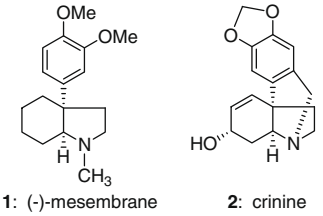
However, the chiral induction obtained under various dehydration conditions was found to be only ca. 1:1, and the diastereomers of **5** were not separable.

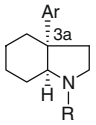
In order to improve the selectivity in the cyclization step, we decided to attempt an intramolecular amide-carbonyl condensation. Chiral amide precursors **6** have been prepared by coupling **4** with the commercially available chiral amines using 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)/*N*-methylmorphorine *N*-oxide (NMM) in good yields.[8] The following asymmetric cyclization to **7** has been found to be optimal 65 °C in benzene in the presence of catalytic amount of TsOH. Higher temperature reduced the selectivity and even yields due to some decomposition, and the lower temperature showed only retarded reaction process without enhancing the selectivity. 1-(1-Naphthyl)ethyl group on the nitrogen provided the best ratio 3:1 in quantitative yield, however, as an inseparable diastereomeric mixture. It seems that steric interaction between dimethoxyphenyl group and bulkier aromatic groups of amide would play a role for differentiating the two carbonyl groups in the reaction with the amide (Table 1).

Conversion of compound **7a** to the known intermediate **10** for (−)-mesembrane has been carried out by reducing the carbonyl to alcohol and transforming the alcohol to xanthate **8** in 95% in two steps.[9] Reduction of the xanthate to inseparable hexahydroindol-2-ones **9** by Bu_3SnH/AIBN was achieved in 84% yield. Fortunately, each reaction provided the inseparable products in good



Scheme 1.





3: cis-3a-aryloctahydroindole ring skeleton

Figure 1.

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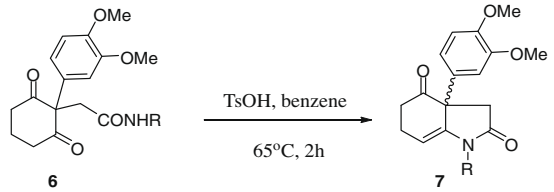
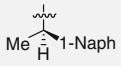
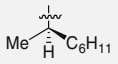
doi:10.1016/j.tetlet.2010.02.136

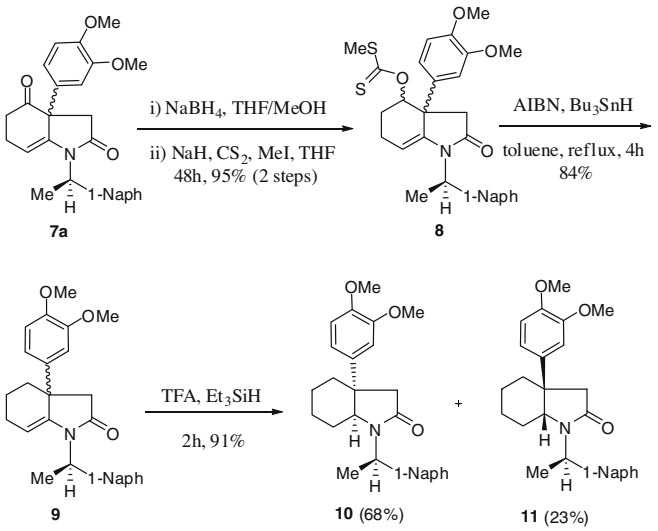
Table 1



6 7

Entry	R	Yield (%)	Ratio of **7**[a]
1		99	3:1
2		97	2.4:1
3		82	1.2:1
4		83	1.1:1

[a] Ratios were detected by ^{1}H NMR.



Scheme 2.

yields without change of the diastereomeric ratio. Reduction of **9** with Et_3SiH[4c] provided octahydroindol-2-one **10** as a major product (68%) and its isomer **11** as a minor product (23%). The spectral data[10] of these compounds were identical to those published in the literature[4c] {**10**: $[\alpha]_D^{30}$ 64.2, lit. $[\alpha]_D^{26}$ 65.6; **11**: $[\alpha]_D^{30}$ −71.4, lit. $[\alpha]_D^{26}$ −73.0} (Scheme 2).

We have tried to differentiate the enantiotopic 1,3-dicarbonyl groups of 1,3-cyclohexanedione by asymmetric cyclodehydration process for the synthesis of chiral mesembrane. In the intramolecular condensation process, marginal selectivity has been found, and the subsequent conversion to the known intermediates confirmed each of the structures and ensued the formal synthesis of (−)-mesembrane.

Acknowledgment

This work was supported by the Korea Research Foundation Grant funded by Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2008–313-C00461).

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5. Compound **4** has been prepared by modifying the known process[4a,6] coupling 1,3-cyclohexadione with 4-bromoveratrole in the presence of $Pd(OAc)_2$ (0.01 equiv) and (2-biphenyl)di-*tert*-butylphosphine (0.02 equiv) (81% yield), O-allylation with allylbromide followed by Claisen rearrangement (86% yield), and oxidative cleavage to carboxylic acid **4** by $NaIO_4/KMnO_4$ (65% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (^{1}H, d, J = 8.4 Hz), 6.63–6.55 (2H, m), 3.86 (3H, s, OMe), 3.83 (3H, s, OMe), 3.22 (2H, s), 2.78–2.62 (4H, m br), 1.98–1.84 (2H, m br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 177.0, 149.7, 148.9, 126.8, 119.1, 111.7, 109.3, 69.9, 55.9, 55.8, 40.6, 38.6, 17.0; IR (neat, cm^{-1}) 2940, 1716, 1697, 1516, 1261, 1150, 1022, 669.
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10. Compound **10**: $[\alpha]_D^{30}$ 64.2 (*c* 1.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, d, J = 8.0 Hz), 7.83 (1H, d, J = 8.0 Hz), 7.77 (1H, m), 7.58–7.38 (4H, m), 6.98 (1H, dd, J = 2.0, 8.4 Hz), 6.92 (1H, d, J = 2.0 Hz), 6.85 (1H, d, J = 8.4 Hz), 6.06 (1H, q, J = 6.8 Hz), 3.94 (3H, s, OMe), 3.89 (3H, s, OMe), 3.53 (1H, dd, J = 5.6, 8.4 Hz), 2.80 (1H, d, J = 16.4 Hz), 2.61 (1H, d, J = 16.4 Hz), 1.80–1.60 (2H, m), 1.43–1.36 (1H, m), 1.2–1.1 (1H, m), 1.11 (3H, d, J = 6.8 Hz), 0.95–0.68 (3H, m), 0.53–0.47 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 148.8, 147.7, 139.1, 136.5, 133.4, 132.3, 128.6, 128.5, 126.7, 125.8, 124.8, 124.0, 123.6, 118.6, 110.8, 110.2, 61.6, 56.2, 55.9, 45.28, 45.26, 39.8, 35.5, 29.1, 22.1, 21.6, 15.6; IR (neat, cm^{-1}) 3048, 2935, 2859, 1675, 1520, 1453, 1416, 1255, 1027, 808, 780, 731. Compound **11**: $[\alpha]_D^{30}$ −71.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, d, J = 8 Hz), 7.72 (1H, d, J = 8 Hz), 7.54 (1H, d, J = 6.8 Hz), 7.43 (1H, m), 7.36–7.29 (2H, m), 7.02 (1H, m), 6.36 (1H, dd, J = 2.8, 8.4 Hz), 6.26 (1H, d, J = 8.4 Hz), 6.10 (1H, d, J = 2.8 Hz), 5.98 (1H, q, J = 7.2 Hz), 3.76 (3H, s, OMe), 3.45 (3H, s, OMe), 2.97 (1H, dd, J = 6, 9.2 Hz), 2.80 (1H, d, J = 16.4 Hz), 2.67 (1H, d, J = 16.4 Hz), 2.05 (1H, m), 1.72 (3H, d, J = 6.8 Hz), 1.72–1.16 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 148.1, 147.1, 138.2, 134.4, 133.3, 131.6, 128.6, 127.9, 126.1, 125.4, 124.4, 123.8, 123.0, 117.2, 109.9, 108.7, 61.5, 55.5, 55.3, 46.3, 44.5, 39.8, 36.4, 31.0, 22.6, 21.9, 18.5; IR (neat, cm^{-1}) 2932, 2857, 1678, 1520, 1411, 1254, 1151, 1028, 804, 779.