Simple syntheses of marine alkaloid, (±)-helonin A, and its analogs

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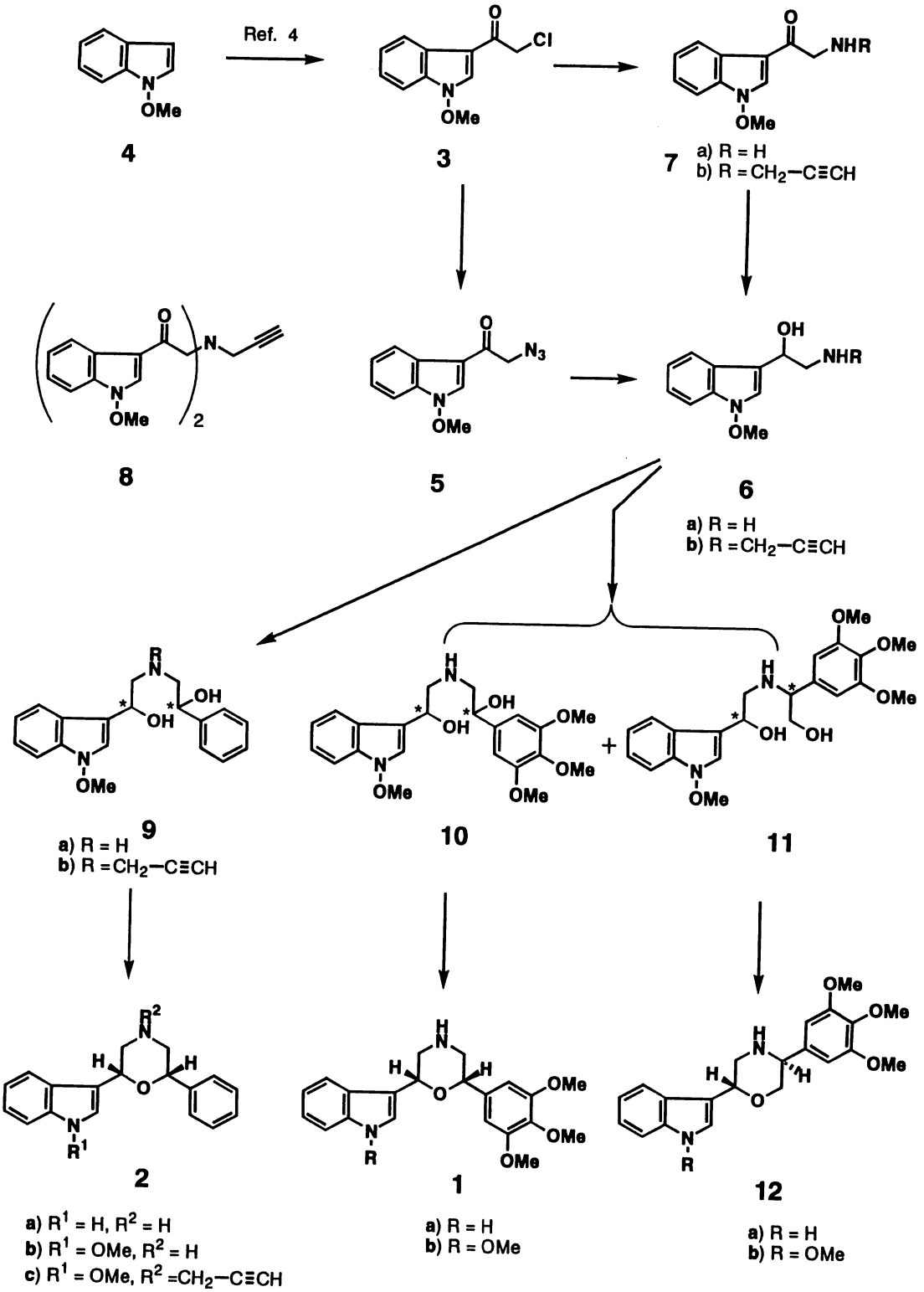
SIMPLE SYNTHESES OF MARINE ALKALOID, (±)-CHELONIN A, AND ITS ANALOGS[1]

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Abstract----The first total synthesis of (±)-chelonin A and syntheses of its analogs are achieved based on 1-hydroxyindole chemistry.

Chelonin A (**1a**, Scheme 1), was isolated from marine sponge *Chelonaplysilla* sp. and determined by D. J. Faulkner and co-workers.[2] They also reported its potent antimicrobial and antiinflammatory activities.[2] In this communication, we wish to report the first and simple total synthesis of (±)-**1a** and syntheses of its analogs based on 1-hydroxyindole chemistry.[3] First, we tried the synthesis of model compounds, 2,6-*cis*-2-(indol-3-yl)-6-phenylmorpholine (**2a**) and 2,6-*cis*-2-(1-methoxyindol-3-yl)-6-phenyl-*N*-propargylmorpholine (**2c**). 3-(2-Chloroacetyl)-1-methoxyindole[4] (**3**), available from 1-methoxyindole (**4**), was converted to 3-(2-azidoacetyl)-1-methoxyindole (**5**) in 87% yield by treatment with NaN_3 in CH_3CN-H_2O for 2 h under reflux. Reduction of **5** with $LiAlH_4$ in THF for 1 h at room temperature afforded **6a** in 48% yield. The compound (**6a**) was alternatively produced in 72% yield by the reduction of 3-(2-aminoacetyl)-1-methoxyindole[4] (**7a**) with $NaBH_4$ in MeOH for 1 h at room temperature. When **3** was reacted with propargyl amine (excess) in MeOH for 1 h under reflux, monomer (**7b**) and dimer (**8**) were produced in 53% and 32% yields, respectively. Reduction of **7b** with $NaBH_4$ in MeOH for 8 h at room temperature afforded 57% yield of

Scheme 1


Ref. 4
4
3
7
a) R = H
b) R = CH2—C≡CH
8
5
6
a) R = H
b) R = CH2—C≡CH
9
a) R = H
b) R = CH2—C≡CH
10
11
2
a) R1 = H, R2 = H
b) R1 = OMe, R2 = H
c) R1 = OMe, R2 = CH2—C≡CH
1
a) R = H
b) R = OMe
12
a) R = H
b) R = OMe

6b. Subsequent reaction of **6a** with styrene oxide in CH_3CN for 24 h under reflux produced **9a** as a 1:1 mixture of diastereoisomers in 57% yield. Similar reaction of **6b** with styrene oxide afforded **9b** as a 1:1 mixture of diastereoisomers in 80% yields.

Treatments of **9a** and **9b** with 2N HCl in MeOH for 1 h or 20 min at room temperature smoothly underwent cyclization to give the desired **2b** and **2c** as a single isomer in both cases, in 74 or 70% yields, respectively. The ^{1}H-nmr spectrum of **2b** shows the presence of two sets of H_{axial}-H_{axial} coupling (J=10.6 Hz), which clearly proves that phenyl and 1-methoxyindol-3-yl substituents are *cis* and equatorial. Similarly, the stereochemistry of **2c** are proved to be *cis* and both substituents are equatorial. Catalytic hydrogenation of **2b** over 10% Pd/C at room temperature and 1 atm for 4 h produced **2a** in 51% yield.

Based on the successful model experiments, **6a** was next treated with 3,4,5-trimethoxystyrene oxide[5] under the similar reaction conditions as described above to give the regioisomers, **10** and **11**, in 19 and 21% yields, respectively. Acid cyclizations of **10** and **11** formed the corresponding **1b** and **12b** in 89 and 81% yields, respectively. One pot preparations of **1b** and **12b** from **6a** were realized in 16 and 15% overall yields, respectively, when the reactions of **6a** with the epoxide and acid cyclization were carried out successively. Catalytic hydrogenation of **1b** over 10% Pd/C at room temperature and 1 atm for 4 h produced **1a** in 59% yield, while the same reaction of **12b** afforded **12a** in 57% yield.

Spectral data of natural product[2] (**1a**) are identical with those of (±)-**1a** and not with those of (±)-**12a**. Thus, the structure of chelonin A was alternatively proved by chemical synthesis. 3,4,5-Trimethoxyphenyl and indol-3-yl substituents of **12a** are proved to be *trans* and equatorial, based on its ^{1}H-nmr spectrum showing two sets of H_{axial}-H_{axial} coupling (J=10.3 and 11.4 Hz).

In summary, we have developed a simple method which can produce various

chelonin analogs only by changing epoxide components. Since optically active epoxides are available, syntheses of chiral chelonin analogs are currently in progress.

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   All new compounds gave satisfactory spectral and elemental analysis for crystals or high resolution mass spectral data for oil. **1a**) mp 161-162°C (decomp.); **1b**) oil; **2a**) hard oil; **2b**) hard oil; **2c**) oil; **5**) mp 69-70°C; **6a**) mp 126-127°C (decomp.); **6b**) mp 95-96°C; **7b**) mp 76-77°C; **8**) mp 173-174°C; **10**) oil; **11**) oil; **12a**) mp 155-159°C; **12b**) mp 124-126°C.
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5. 3,4,5-Trimethoxystyrene oxide was prepared from 3,4,5-trimethoxybenzaldehyde in 56% yield by the reaction with dimethylsulfoxonium methylide.

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