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

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

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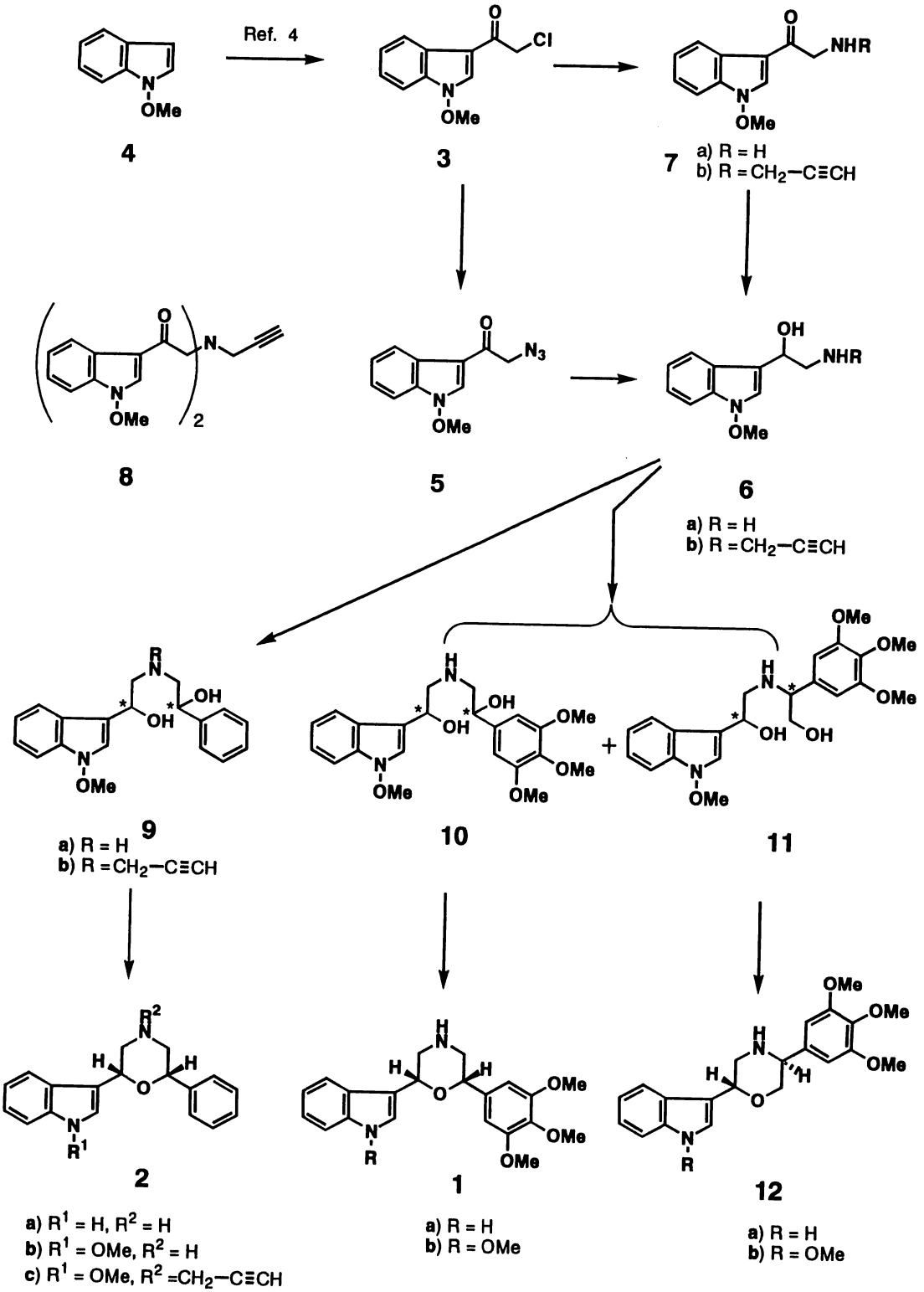
Abstract----The first total synthesis of (±)-chelonin A and syntheses of its analogs are achieved based on 1-hydroxyindole chemistry.

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.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

1. This is partly reported, Abstracts of Papers, 2, The 114th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, March, 1993, p. 109. This report is Part 72 of a series entitled "The Chemistry of Indoles". Part 71: M. Somei, K. Kobayashi, K. Tanii, T. Mochizuki, Y. Kawada, and Y. Fukui, *Heterocycles*, 1995, **40**, No. 1, in press.
   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.
2. S. C. Bobzin and D. J. Faulkner, *J. Org. Chem.*, 1991, **56**, 4403.
3. a) T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, *Heterocycles*, 1991, **32**, 221; b) M. Somei, T. Kawasaki, Y. Fukui, F. Yamada, T. Kobayashi, H. Aoyama, and D. Shinmyo, *ibid.*, 1992, **34**, 1877; c) F. Yamada, Y. Fukui, D. Shinmyo, and M. Somei, *ibid.*, 1993, **35**, 99; d) M. Somei and Y. Fukui, *ibid.*, 1993, **36**, 1859; e) Review: M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1991, **49**, 205.
4. M. Somei, H. Sato, N. Komura, and C. Kaneko, *Heterocycles*, 1985, **23**, 1101 and references cited therein.
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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