HETEROCYCLES, Vol 26, No 7, 1987

A FORMAL SYNTHESIS OF N-ACETYL-L-ACOSAMINE

Tetsuji Kametani,* Yukio Suzuki, Chieko Ban, Kiyoshi Kanada, and
Toshio Honda
Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41
Shinagawa-ku, Tokyo 142, Japan

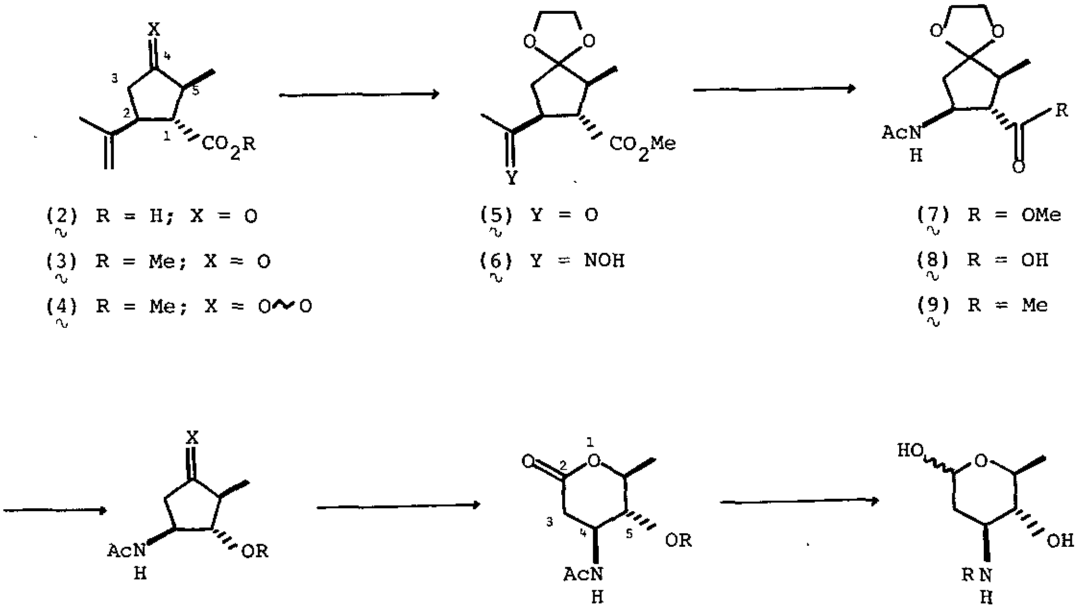
Abstract ———— N-Acetyl-L-acosamine (1a) was formally synthesized from optically active cyclopentane derivative (2), which was easily derived from (S)-(+)-carvone.

Both enantiomers of acosamine[1] (1b) are known to be structural components of glycosidic and polysaccharide antibiotics, and many synthetic methods, especially for the L-enantiomorph of acosamine (1b), were reported owing to the investigation of the structure-activity relationship on daunorubicin analogues as anticancer agents. Recently we have reported[2] the synthesis of an optically active cyclopentane derivative (enantiomer of 2) from (R)-(-)-carvone, successful utilization of which is shown in synthesis of monoterpene alkaloid, tecomanine. The cyclopentane derivative (2), easily prepared from commercially available (S)-(+)-carvone, is also expected to be a useful synthon of a large number of natural product possessing a cyclopentane or a δ-lactone moiety.

We wish to report here a synthesis of δ-lactone derivative (13), which was already converted[3] into L-acosamine derivative (1a), from the compound (2).

The keto-acid (2), derived from (S)-(+)-carvone by the same procedure described for synthesizing the enantiomorph of 2, was esterified by treatment with methanol in the presence of dicyclohexylcarbodiimide to give 3[4] in 94 % yield. After ketalization of 3 in usual manner, ozonolysis of the resultant compound (4) was carried out to afford the ketone (5). Treatment of 5 with hydroxylamine hydrochloride in the presence of pyridine produced the anti-oxime (6) predominantly, which was converted into the amide (7) in 68.3 % yield from 3 by Beckmann rearrangement with phosphoryl chloride in pyridine. Hydrolysis of the compound (7) with sodium hydroxide in refluxing methanol gave the corresponding carboxylic acid (8). Although difficulties were initially encountered in the introduction of an oxygen functionality at the position of the carboxyl group under various reaction conditions, such as oxidative decarboxylation with lead tetraacetate in acetic acid or Baeyer-Villiger oxidation through the corresponding mixed anhydride, the desired acetoxy compound (10) was obtained by the Baeyer-Villiger oxidation with m-chloroperbenzoic acid in refluxing dichloromethane of the ketone (9) which was derived from 8 by the reaction with methyl lithium. Hydrolysis of 10 with potassium carbonate in methanol furnished the alcohol (11), and subsequent deprotection of the ketal moiety by p-toluenesulfonic acid in acetone gave the ketone (12). Finally the compound (12) was converted into the desired compound (13)^3 by the oxidation with m-chloroperbenzoic acid in dichloromethane in 49 % yield from 7. In order to ensure the stereochemistry the compound (13) was acetylated in a usual manner and the spectral data of the resultant N,O-diacetylated compound (14) were well agreed with those of dl-14 reported by Ito and his co-workers.^{5}

Thus we succeeded in the synthesis of L-acosamine derivative from readily available (S)-(+)-carvone and this synthesis demonstrated that both enantiomorphs of 2 can play as useful synthons in the synthesis of a variety of natural products.



(2) R = H; X = O
(3) R = Me; X = O
(4) R = Me; X = O~O

(5) Y = O
(6) Y = NOH

(7) R = OMe
(8) R = OH
(9) R = Me

(10) R = Ac; X = O~O
(11) R = H; X = O~O
(12) R = H; X = O

(13) R = H
(14) R = Ac

(1a) R = Ac
(1b) R = H

ACKNOWLEGEMENT

We thank Dr. H. Kasai for manuscript preparation for her kind assistance.

REFERENCES

1. F. M. Hauser and Z. R. Ellenberger, Chem. Rev., 1986, **86**, 35 and references cited therin.
2. T. Kametani, Y. Suzuki, C. Ban, and T. Honda, Heterocycles, in press.
3. I. Dyong and H. Bendlin, Chem. Ber., 1978, **111**, 1677.
4. All compounds reported here included a small amount of diastereoisomers which could not be separated. Crystalline compounds were obtained as single stereoisomers by recrystallization.
    - **4** : $\nu_{max}^{CHCl_3}$ cm^{-1} 1720, 1635; δ(60 MHz, CCl_4) 0.93 (3H, br d, J = 6 Hz, CH_3), 1.70 (3H, s, CH_3), 3.63 (3H, s, OCH_3), 3.87 (4H, s, OCH_2CH_2O), 4.71 (2H, br s, $C{=}CH_2$); m/z 240 (M^+).
    - **5** : $\nu_{max}^{CHCl_3}$ cm^{-1} 1720; δ(60 MHz, CCl_4) 0.84 and 1.00 (total 3H, each d, J = 6 Hz, CH_3), 2.10 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 3.90 (4H, s, OCH_2CH_2O); m/z 242 (M^+).
    - **6** : $\nu_{max}^{CHCl_3}$ cm^{-1} 3300, 1720; δ(60 MHz, $CDCl_3$) 1.00 (3H, d, J = 6.5 Hz, CH_3), 1.87 (3H, s, CH_3), 2.73 (3H, s, OCH_3), 3.98 (4H, s, OCH_2CH_2O), 8.95 (1H, br s, OH); m/z 257 (M^+).
    - **7** : $\nu_{max}^{CHCl_3}$ cm^{-1} 3420, 1725, 1665; δ(100 MHz, $CDCl_3$) 0.97 and 1.00 (total 3H, each d, J = 4.1 Hz, CH_3), 1.66 (1H, dd, J = 14 Hz, 4 Hz, C_3-H), 1.94 and 1.95 (total 3H, each s, CH_3), 3.70 and 3.72 (total 3H, each s, OCH_3), 3.84-4.05 (4H, m, OCH_2CH_2O), 4.36-4.68 (1H, m, C_2-H), 6.08 (1H, br s, NH); m/z 257 (M^+).
    - **9** : mp 84.5-85.5°C; $[\alpha]_D$ -25.5° (c = 0.58, $CHCl_3$); $\nu_{max}^{CHCl_3}$ cm^{-1} 3400, 1705, 1655; δ (100 MHz, $CDCl_3$) 0.94 (3H, d, J = 6.4 Hz, CH_3), 1.71 (1H, dd, J = 14 Hz, 4.5 Hz, C_3-H), 1.96 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.93 (4H, s, OCH_2CH_2O), 4.20-4.56 (1H, m, C_2-H), 7.04 (1H, br d, J = 8 Hz, NH); m/z 241 (M^+).
    - **10** : $\nu_{max}^{CHCl_3}$ cm^{-1} 3400, 1715, 1655; δ(100 MHz, $CDCl_3$) 0.98 (3H, d, J = 6.9 Hz, CH_3), 1.67 (1H, dd, J=14.3 Hz, 6.2 Hz, C_3-H), 1.95 (3H, s, CH_3), 2.09 (3H, s, CH_3), 3.93 (4H, s, OCH_2CH_2O), 4.08-4.54 (1H, m, C_2-H), 4.73 (1H, dd, J = 9.8 Hz, 6.9 Hz, C_1-H), 6.25 (1H, br s, NH); m/z 257 (M^+).
    - **11** : mp 161-162°C; $[\alpha]_D$ +30.7° (c = 0.6, MeOH); $\nu_{max}^{CHCl_3}$ cm^{-1} 3330, 1655; (400 MHz,

$CDCl_3$) 1.02 (3H, d, J = 6.8 Hz, CH_3), 1.62 (1H, dd, J = 14.2 Hz, 6.1 Hz, C_3-H), 2.00 (3H, s, CH_3), 2.03-2.11 (1H, m, C_5-H), 2.39 (1H, dd, J = 14.2 Hz, 10 Hz, C_3-H), 3.55 (1H, dd, J = 9.8 Hz, 6.1 Hz, C_1-H), 3.85-3.97 (4H, m, OCH_2CH_2O), 4.50 (1H, br s, C_2-H), 6.02 (1H, br s, NH); m/z 215 (M^+).

12 : $[\alpha]_D$ +93.1° (c = 0.26, MeOH); $\nu_{max}^{CHCl_3}$ cm^{-1} 3300, 1740, 1655; δ(60 MHZ, $CDCl_3$) 1.15 (3H, d, J = 7 Hz, CH_3), 2.03 (3H, s, CH_3) 2.90 (1H, ddd, J = 18 Hz, 8.7 Hz, 2 Hz, C_3-H), 3.82 (1H, dd, J = 18 Hz, 8 Hz, C_1-H), 4.00-4.43 (1H, m, C_2-H), 5.17 (1H, br s, OH), 6.16 (1H, br s, NH); m/z 171 (M^+).

13 : mp 142-143°C; $[\alpha]_D$ +1.4° (c = 1.0, MeOH); $\nu_{max}^{CHCl_3}$ cm^{-1} 3300, 1710, 1660; δ(60 MHz, CD_3OD) 1.45 (3H, d, J = 6.3 Hz, CH_3), 2.00 (3H, s, CH_3), 2.50 (1H, dd, J = 18 Hz, 7.5 Hz, C_3-H), 3.10 (1H, dd, J = 18 Hz, 7 Hz, C_3-H), 3.47 (1H, t, J = 8 Hz, C_5-H), 4.03-4.60 (2H, m, C_4-H and C_6-H).

Satisfactory elemental analyses were obtained for these compounds.

5. M. Hirama, T. Shigemoto, Y. Yamataki, and S. Ito, Tetrahedron Lett., 1985, **26**, 4133.

Received, 16th April, 1987