Pergamon

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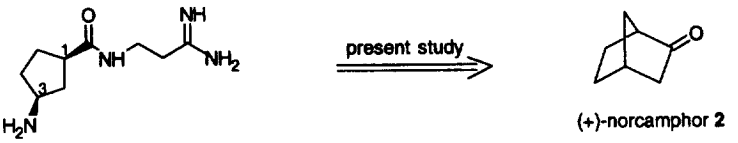
A convenient enantioselective synthesis of natural (1*R*,3*S*)-amidinomycin

Hiroshi Nagata, Takahiko Taniguchi and Kunio Ogasawara *
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

Abstract: Natural (1*R*,3*S*)-amidinomycin, an antiviral metabolite isolated from *Streptomyces* species, has been synthesized conveniently from (+)-norcamphor in an enantioselective manner. © 1997 Published by Elsevier Science Ltd

(1*R*,3*S*)-Amidinomycin **1** is an antiviral antibiotic metabolite isolated in Japan from the culture filtrate of *Streptomyces* species.[1] Its absolute structure was determined by X-ray crystallographic analysis[2] and was confirmed by the enantioselective synthesis.[3] Since its first enantioselective synthesis by Chenevert and co-workers,[3] two enantioselective syntheses, one formal by Trost and co-workers[4] and one total by Sung and Frahm,[5] have so far been reported. In connection with our synthetic project[6] utilizing optically active norcamphor **2** for the enantiocontrolled construction of natural products, we explored the synthesis of amidinomycin **1** using optical active norcamphor **2**. Herein, we would like to report a convenient enantioselective synthesis of natural (1*R*,3*S*)-amidinomycin **1** starting from (+)-norcamphor (+)-**2** (Scheme 1).



(1*R*,3*S*)-amidinomycin **1**

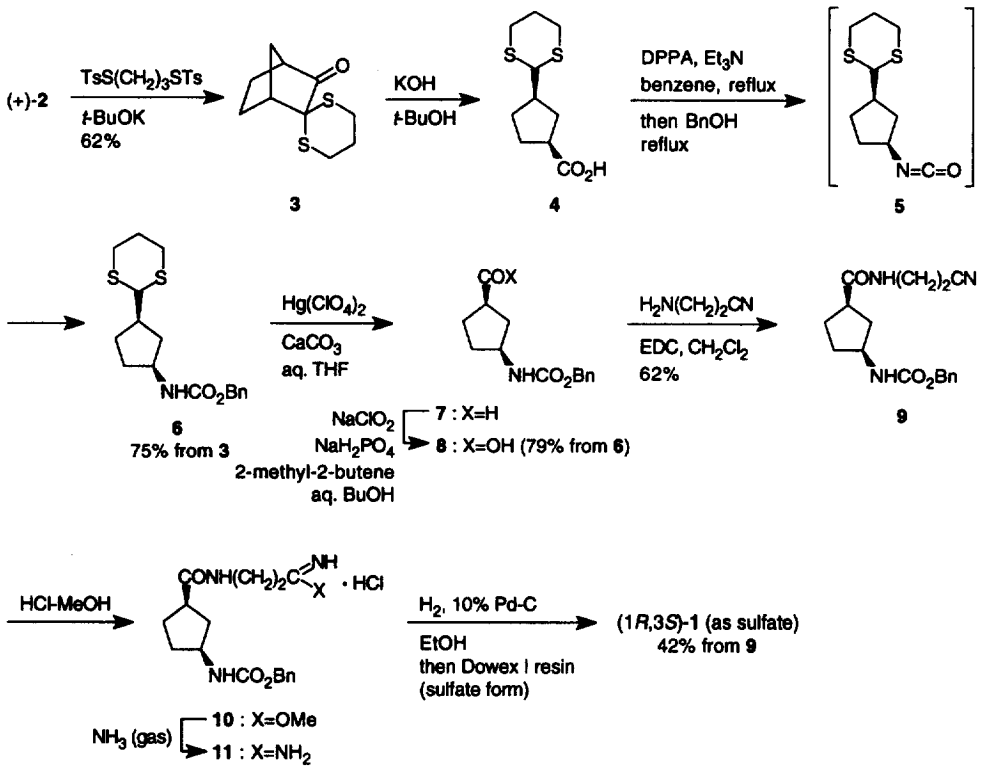
(+)-norcamphor **2**

Scheme 1.

Treatment of (+)-norcamphor[7] (+)-**2** with trimethylene dithiotosylate[8] in the presence of potassium *tert*-butoxide furnished the α-diketone monothioketal **3**, $[\alpha]_D^{27}$ +147.1 (*c* 1.0, $CHCl_3$), in 62% yield (Scheme 2). Exposure of **3** to potassium hydroxide in warm *tert*-butanol initiated cleavage[8,9] of the α-diketone monothioketal functionality to give the dithiane acid **4** which was immediately reacted with diphenylphosphoryl azide[10] (DPPA) in refluxing benzene containing triethylamine followed by benzyl alcohol to afford the benzyl carbamate **6**, mp 104–106°C, $[\alpha]_D^{27}$ −11.1 (*c* 1.1, $CHCl_3$), *via* the transient isocyanate **5**. Overall yield of the carbamate **6** from the acid **4** was 75%. Hydrolysis of **6** with mercury(II) perchlorate in aqueous tetrahydrofuran (THF) containing calcium carbonate[11] gave the aldehyde **7** which without purification was oxidized with aqueous sodium perchlorate in the presence of 2-methyl-2-butene[12] to give the carboxylic acid **8**, mp 64–65°C, $[\alpha]_D^{29}$ −1.9 (*c* 1.1, $CHCl_3$), in 79% overall yield. The acid **8** was condensed with 3-aminopropionitrile in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide[3] (EDC) in dichloromethane to give the amide **9**, mp 136–138°C, $[\alpha]_D^{31}$ +10.3 (*c* 1.2, $CHCl_3$), having the requisite carbon framework, in 62% yield. In order to obtain the target molecule, **9** was first treated with methanolic hydrogen chloride[3,5] to form the iminoether hydrochloride **10** which then was exposed to ammonia gas to give the amidine hydrochloride **11**. Finally, the hydrochloride **11** was subjected to hydrogenolysis on palladized charcoal

* Corresponding author. Fax +81-22-217-6845; Email konol@mail.cc.tohoku.ac.jp

under medium pressure of hydrogen (5 atm) to remove the carbamate group to afford (1*R*,3*S*)-amidinomycin[13] **1** as sulfate, mp 289–291°C (decomp.), $[\alpha]_D^{29}$ −3.5 (*c* 0.5, H_2O) {natural:[1d] mp 289–291°C (decomp.), $[\alpha]_D^{21}$ −3.9 (*c* 3.0, H_2O)}, after purification using ion exchange resin[5] (Dowex I, sulfate form), followed by recrystallization from aqueous methanol. Spectral data (IR and ^1H NMR) of the product were identical with those reported for the synthetic (1*R*,3*S*)-amidinomycin **1** sulfate.[5] Overall yield of (1*R*,3*S*)-amidinomycin **1** sulfate from the amide **9** was 42%.



Scheme 2.

In summary, we have developed a convenient synthesis of natural (1*R*,3*S*)-amidinomycin starting from (+)-norcamphor in 9.6% overall yield involving six isolation stages.

Acknowledgements

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References

1. (a) Kikuchi, K. *J. Antibiot.* **1955**, *8*, 145. (b) Kuroya, M.; Hinuma, Y. *Jap. J. Microbiol.* **1957**, *1*, 85. (c) Kobayashi, N. *Tohoku J. Exptl. Med.* **1959**, *70*, 95. (d) Nakamura, S.; Umezawa, H. *J. Antibiot.* **1960**, *13*, 362. (e) *idem ibid.* **1961**, *14*, 163. (f) Nakamura, S. *Chem. Pharm. Bull.* **1961**, *9*, 641.
2. Kaneda, M.; Nakamura, S.; Iitaka, Y. *J. Antibiot.* **1980**, 778.
3. Chenevert, R.; Lavoie, M.; Courchesne, G.; Martin, R. *Chem. Lett.* **1994**, 93.
4. Trost, B. M.; Stenkamp, D.; Pulley, S. R. *Chem. Eur. J.* **1995**, *1*, 568.
5. Sung, S.-Y.; Frahm, A. W. *Arch. Pharm. Med. Chem.* **1996**, *329*, 291.
6. Kawamura, M.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 3369. Saito, M.; Kawamura, M.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 9003. Kawamura, M.; Ogasawara, K. *J. Chem. Soc.*,

Chem. Commun. **1995**, 2403. Kawamura, M.; Ogasawara, K. *Heterocycles* **1997**, *44*, 129. Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1997**, 765.

7. Prepared from (+)-*endo*-norborneol (ca. 95% ee) kindly provided by the Chisso Corporation, Japan.
8. Takano, S.; Hiroya, K.; Ogasawara, K. *Chem. Lett.* **1983**, 255. Takano, S.; Ogasawara, K. *J. Synth. Org. Chem. Jpn.* **1977**, *35*, 795.
9. Marshall, J. A.; Seitz, D. E. *J. Org. Chem.* **1974**, *39*, 1814.
10. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
11. Bernardi, R.; Ghiringhelli, D. *J. Org. Chem.* **1987**, *52*, 5021.
12. Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.
13. Spectral data of the synthetic materials: **3** — IR (film): ν=1742 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.49 (dt, 1H, *J*=1.3, 10.7 Hz), 1.56–1.80 (m, 2H), 1.80–1.95 (m, 2H), 2.12–2.24 (m, 2H), 2.46 (m, 1H), 2.50–2.66 (m, 3H), 2.73 (m, 1H), 3.37 (ddd, 1H, *J*=2.5, 12.9, 14.3 Hz), 3.75 (ddd, 1H, *J*=2.5, 12.9, 13.7 Hz). HRMS: Calcd for $C_{10}H_4OS_2$: 214.0485. Found: 214.0468. **6** — IR (Nujol): ν=3304, 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.33–1.58 (m, 2H), 1.62–2.24 (m, 4H), 2.11 (m, 1H), 2.20–2.37 (m, 2H), 2.77–2.92 (m, 4H), 4.02 (m, 1H), 4.04 (d, 1H, *J*=6.9 Hz), 4.78 (br s, 1H), 5.09 (br s, 2H), 7.28–7.40 (m, 5H). MS: *m/z*=337 (M^+), 246 (100%). HRMS: Calcd for $C_{17}H_{23}NO_2S_2$: 337.1203. Found: 337.1143. Anal. Calcd for $C_{17}H_{23}NO_2S_2$: C 60.50, H 6.87, N 4.15. Found: C 60.30, H 6.81, N 4.01. **8** — IR (Nujol): ν=3326, 1701 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.62 (m, 1H), 1.74 (dt, 1H, *J*=7.5, 12.9 Hz), 1.90–2.04 (m, 2H), 2.27 (br dt, 1H, *J*=9.0, 12.0 Hz), 2.85 (m, 1H), 3.99 (m, 1H), 5.09 (br s, 2H), 7.45–7.52 (m, 2H), 7.60 (m, 1H), 8.02–8.08 (m, 2H). MS: *m/z*=263 (M^+), 91 (100%). HRMS: Calcd for $C_{14}H_{17}O_4N$: 263.1157. Found: 263.1159. **9** — IR (Nujol): ν=3314, 2246, 1680, 1650 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.72–2.03 (m, 5H), 2.09 (m, 1H), 2.61 (t, 2H, *J*=6.3 Hz), 2.69 (m, 1H), 3.47 (dt, 2H, *J*=6.1, 6.3 Hz), 4.15 (m, 1H), 5.06 (d, 1H, *J*=12.4 Hz), 5.12 (d, 1H, *J*=12.4 Hz), 5.99 (br s, 1H), 6.28 (br s, 1H), 7.28–7.41 (m, 5H). MS: *m/z*=315 (M^+), 91 (100%). HRMS: Calcd for $C_{17}H_{21}O_3N_3$: 315.1582. Found: 315.1568. **1** — IR (KBr): ν=1656, 1637, 1119, 620 cm^{-1}. ^{1}H NMR (D_2O): δ=1.78–1.96 (m, 3H), 2.00–2.20 (m, 2H), 2.33 (ddd, 1H, *J*=6.8, 7.4, 14.6 Hz), 2.69 (t, 1H, *J*=6.6 Hz), 2.93 (m, 1H), 3.58 (t, 1H, *J*=6.3 Hz), 3.77 (m, 1H). MS (FAB): *m/z*=199 (M^++1), 297 (M^++1+H_2SO_4), 319 (M^++H_2SO_4+Na).

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