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STEREOSELECTIVE SYNTHESIS OF THE SYNTHONS HAVING THREE CONSECTIVE CHIRAL CENTERS

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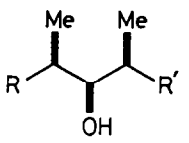
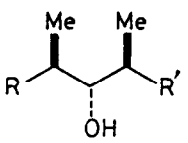
Summary: Four possible diastereomers having three consective chiral centers, R-CHMe-CHOH-CHMe-R', have been synthesized stereoselectively based on the stereoselective reduction of acyclic ketones.

1,3-Dimethyl-2-hydroxy unit, R-CHMe-CHOH-CHMe-R', having three consective chiral centers is an important synthon for the synthesis of polyoxo antibiotics such as monensin and rifamycins. The excellent methods for the stereoselective synthesis of this unit have been developed in connection with the synthetic studies of these antibiotics.[1]

We now report an alternative method for the stereoselective synthesis of four possible diastereomers (A~D) of this unit. The key reactions involved in the present method are the stereoselective reduction of acyclic ketones (i.e., reduction of β-hydroxy ketone,[2] β-keto ester,[3] α-hydroxy ketone,[4] and α-silyloxy ketone[4]) and the regioselective ring-opening of epoxides by 1,3-dithiane anion.



A



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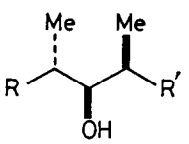

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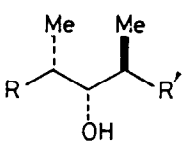


D

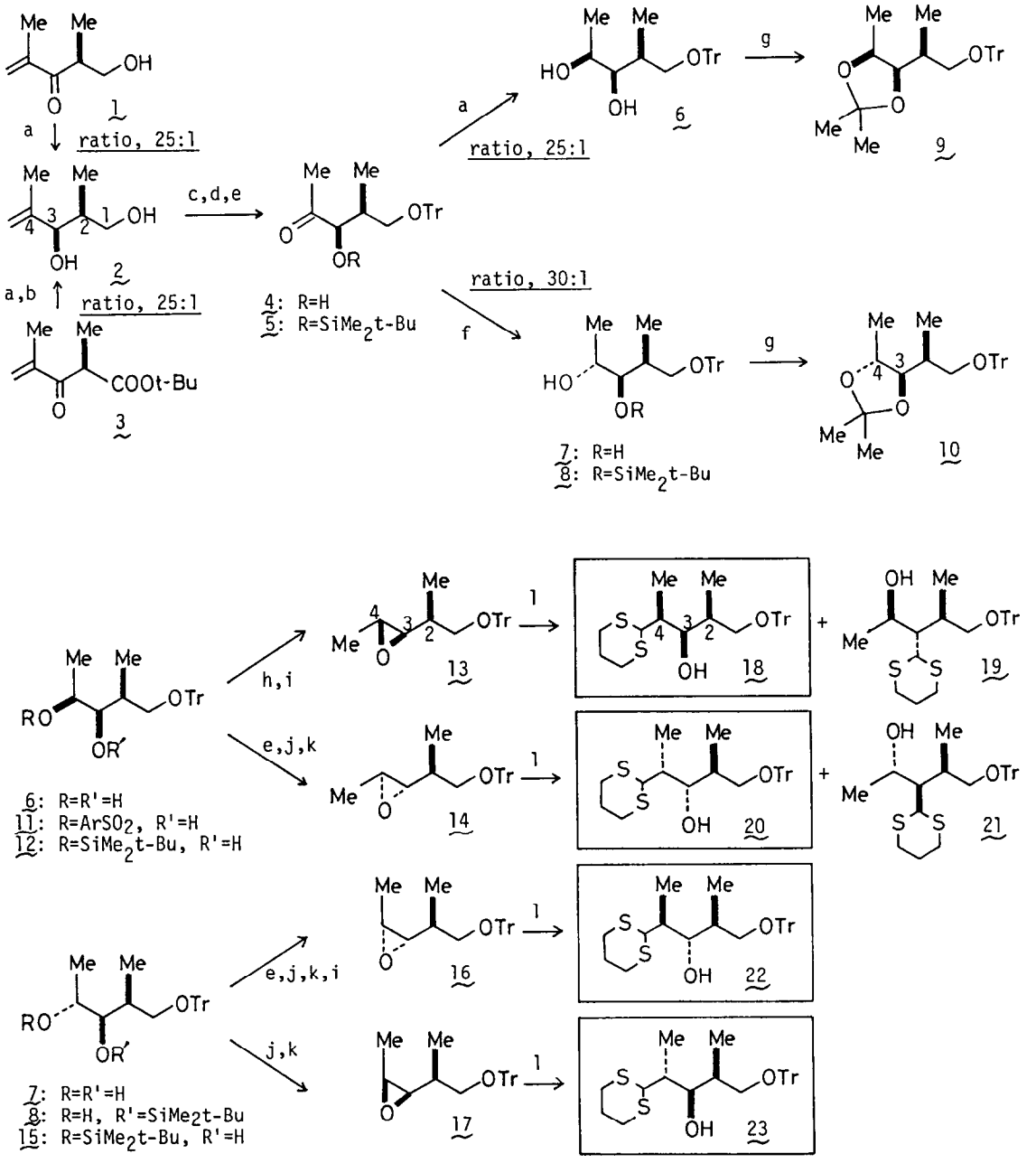
The β-hydroxy-α-methyl ketone 1[5] was reduced with $Zn(BH_4)_2$ in ether at 0°C to produce the erythro-diol 2 [NMR ($CDCl_3$): δ 4.24 (d, J=3.4 Hz; C-3 H)] in 25 : 1 stereoselectivity (91% combined yield). 2 was also prepared from the β-keto ester 3[6] by $Zn(BH_4)_2$ reduction (ratio, 25 : 1; 73% combined yield), followed by $LiAlH_4$ reduction (100%). The erythro-diol 2 was converted to the α-hydroxy ketone 4 [mp 111-112°C; NMR ($CDCl_3$): δ 2.17 (s; Ac), 4.53 (dd, J= 4.6, 2.0 Hz; C-3 H)] by tritylation followed by ozonolysis in 60% yield. Treatment of 4 with t-butyldimethylsilyl chloride gave the 3-silyloxy ketone 5 [mp 82-84°C; NMR ($CDCl_3$): δ 2.09 (s; Ac), 4.12 (d, J=3.7 Hz; C-3 H)] in 99% yield.

The α-hydroxy and α-silyloxy ketones, 4 and 5, were reduced to the erythro- and threo-diols, 6 and 7, respectively, under high stereoselectivity by the method reported in the preceding paper.[4] Thus, $Zn(BH_4)_2$ reduction of the α-hydroxy ketone 4 in ether at 0°C gave the erythro-diol 6 [NMR ($CDCl_3$): δ 3.50 (m; C-3 H), 3.73 (m; C-4 H)] in 25 : 1 stereoselectivity

(99% combined yield). On the other hand, treatment of the α-silyloxy ketone 5[7] with Vitride [$NaAlH_2(OCH_2CH_2OMe)_2$][8] in toluene at -78°C and then room temperature for 15 hr produced the threo-diol 7 [NMR ($CDCl_3$): δ 3.46 (m; C-3 H), 3.74 (m; C-4 H)] in 30 : 1 stereoselectivity (94% combined yield). Complete desilylation took place in this case. Treatment of 5 with Vitride at -78°C for 15 min afforded the threo-3-silyloxy-4-ol 8 [mp 91-94°C; NMR ($CDCl_3$): δ 3.51 (dd, J=5.4, 2.9 Hz; C-3 H)] in 76% yield. Desilylation did not take place but 22% of the starting material 5 was recovered. The fact that the reduction of 4 and 5 proceeded under high stereoselectivity clearly gave the strong supports to the previous assumption that the reduction of α-hydroxy or α-silyloxy ketones having long or branched alkyl group on the α-position would afford the corresponding erythro- or threo-glycols, respectively, in high selectivity.[9] The stereochemistry of both diols 6 and 7 was confirmed on the basis of their nuclear Overhauser effect (NOE) of the corresponding acetonides 9 and 10 prepared from 6 and 7. The observation of NOE on C-3 H (12.3%) upon irradiation of C-4 Me in 10 suggested that C-3 H and C-4 Me should be oriented to the same side of the five-membered ring.[10] No NOE was observed on C-3 H upon irradiation of C-4 Me in 9.[10]

Then, the erythro- and threo-alcohols, 6, 7, and 8, were successfully converted to the cis- and trans-epoxides, 13, 14, 16, and 17. Treatment of 6 with mesitylenesulfonyl chloride gave the 4-arylsulfonyl-3-ol 11 (86%) regioselectively, which was treated with K_2CO_3 to give the trans-β-epoxide 13[11] in 89% yield. Regioselective protection of 6 with t-$BuMe_2SiCl$ gave the 4-silyloxy-3-ol 12 in 94% yield. Mesylation and the successive n-Bu_4NF treatment of 12 afforded the trans-α-epoxide 14[11] in 77% yield. On the other hand, the threo-diol 7 was treated with t-$BuMe_2SiCl$ to give the 4-silyloxy-3-ol 15 (94%) regioselectively, which was converted to the cis-α-epoxide 16[11] in 80% yield by mesylation followed by treatment with n-Bu_4NF and K_2CO_3. Furthermore, mesylation of 8 followed by treatment with n-Bu_4NF produced the cis-β-epoxide 17[11] in 98% yield. The coupling constants (Hz) of the C-3 and C-4 protons of the four epoxides (13: J=2.2; 14: J=2.2; 16: J=4.4; 17: J=4.2) support the structures of trans-epoxides for 13 and 14, and cis-epoxides for 16 and 17.[12]

Finally, the ring-opening of the four epoxides with 1,3-dithiane anion was examined. The reaction of the trans-epoxide 13 with 5 eq. 2-lithio-1,3-dithiane in THF at 5°C for one week produced the desired C-4 adduct 18[13] (68%) and C-3 adduct 19 (15%) along with the recovered 13 (13%). The same ring-opening of the trans-epoxide 14 similarly gave the desired C-4 adduct 20[13] (44%) and C-3 adduct 21 (15%) along with the recovered 14 (38%).[14] On the other hand, treatment of the cis-epoxides 16 and 17 with the same reagent at 5°C for 64 hr gave only the desired C-4 adducts 22[13], mp 134-136°C, and 23[13], mp 138-141°C, in 96% and 82% yields, respectively. There are precedents for this finding; M. Kinoshita et al.[15] have reported that ring-opening of the cis-epoxides proceeds with high regioselectivity. The mechanism for this selectivity is reasonably explained by them. The stereochemistry of the products was determined on the basis of the splitting patterns of their hydroxy methine protons in the 400 MHz NMR (in $CDCl_3$ + D_2O; double doublets for 18, 20, 22, and 23, and double quartets for 19 and 21) and the well-established fact that ring-opening of epoxides with nucleophiles proceeded with inversion of configuration at the attacked position.[16]



a: $Zn(BH_4)_2$/ether/0°C, b: $LiAlH_4$/ether/0°C, c: TrCl/py/rt, d: O_3/MeOH/-78°C; Me_2S/-78°C→rt, e: t-BuMe_2SiCl/imidazole/DMF/rt, f: Vitride/toluene/-78°C→rt (15 hr) or -78°C (15 min), g: $Me_2C(OMe)_2$/TsOH/ether/rt, h: Mesitylenesulfonyl chloride/DMAP/py/benzene/rt, i: K_2CO_3/MeOH/rt, j: MsCl/py/rt, k: n-$Bu_4NF\cdot 3H_2O$/THF/rt, l: 1,3-dithiane/n-BuLi/THF/-20°C (2 hr) and then 5°C (1 week) or 5°C (64 hr)

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References and Notes

1. M. R. Johnson, T. Nakata, and Y. Kishi, Tetrahedron Lett., 4343 (1979); H. Nagaoka and Y. Kishi, Tetrahedron, 37, 3873 (1981); Private communication from Prof. O. Yonemitsu, Hokkaido University, to be reported at 103th Annual Meeting of Pharmaceutical Society of Japan at Tokyo, April, 1983.
2. T. Nakata, Y. Tani, M. Hatozaki, and T. Oishi, in preparation.
3. T. Nakata and T. Oishi, Tetrahedron Lett., 21, 1641 (1980).
4. T. Nakata, T. Tanaka, and T. Oishi, preceding paper.
5. The β-hydroxy ketone 1 was prepared from methacrolein and α-bromo ester by the Reformatsky reaction followed by $LiAlH_4$ reduction and PDC oxidation; cf. reference 2.
6. The β-keto ester 3 was prepared from methacrolein and α-bromo ester by the Reformatsky reaction followed by Swern's oxidation.
7. In the preceding paper,[4] α-(t-butyldiphenylsilyl)oxy ketones were used for the stereoselective Vitride reduction producing threo-diols. In this paper, we chose the α-(t-butyldimethylsilyl)oxy ketone 5 because the yield of the t-butyldiphenylsilylation of 4 was rather low (77%). However, the stereoselectivity in the Vitride reduction of the corresponding α-(t-butyldiphenylsilyl)oxy ketone of 4 was higher (>50 : 1) than that of 5.
8. The commercially available "Vitride" (70% in toluene) was diluted with toluene to 10% solution.
9. See entry 7 and 16 in the preceding paper.[4]
10. The present results were confirmed by NOE difference spectrum.
11. NMR (400 MHz, $CDCl_3$): 13: δ 0.97 (d, J=6.8 Hz; C-2 Me), 1.34 (d, J=5.4 Hz; C-4 Me), 2.56 (dd, J=7.6, 2.2 Hz; C-3 H), 2.95 (dq, J=2.2, 5.4 Hz; C-4 H); 14: δ 0.99 (d, J=7.1 Hz; C-2 Me), 1.30 (d, J=5.1 Hz; C-4 Me), 2.68 (dd, J=7.0, 2.2 Hz; C-3 H), 2.81 (dq, J=2.2, 5.1 Hz; C-4 Hz); 16: δ 1.04 (d, J=6.8 Hz; C-2 Me), 1.28 (d, J=5.6 Hz; C-4 Me), 2.84 (dd, J=9.3, 4.4 Hz; C-3 H), 3.06 (dq, J=4.4, 5.6 Hz; C-4 H); 17: δ 1.09 (d, J=6.8 Hz; C-2 Me), 1.30 (d, J=5.6 Hz; C-4 Me), 2.69 (dd, J=9.3, 4.2 Hz; C-3 H), 3.10 (dq, J=4.2, 5.6 Hz; C-4 H).
12. D. D. Elleman and S. L. Manatt, J. Mol. Spectry, 9, 477 (1962).
13. NMR (400 MHz, $CDCl_3$): 18: δ 1.08 (d, J=6.8 Hz; Me), 1.09 (d, J=6.8 Hz; Me), 3.89 (t, J=5.4 Hz; C-3 H; $+D_2O$), 4.10 (d, J=4.9 Hz; C-5 H); 20: δ 0.80 (d, J=6.8 Hz; Me), 1.08 (d, J=7.1 Hz; Me), 3.88 (dd, J=8.8, 2.4 Hz; C-3 H; $+D_2O$), 4.16 (d, J=8.5 Hz; C-5 H); 22: δ 0.85 (d, J=7.1 Hz; Me), 1.30 (d, J=7.1 Hz; Me), 3.50 (dd, J=9.4, 3.3 Hz; C-3 H; $+D_2O$), 4.68 (d, J=2.4 Hz; C-5 H); 23: δ 0.97 (d, J=7.1 Hz; Me), 0.98 (d, J=7.1 Hz; Me), 3.84 (dd, J=10.0, 1.7 Hz; C-3 H; $+D_2O$), 4.67 (d, J=2.4 Hz; C-5 H).
14. The reaction of the corresponding benzyl ether of 14 with 2-lithio-1,3-dithiane gave the much better yields; the desired C-4 adduct (70%), C-3 adduct (13%), the recovered starting material (11%).
15. M. Nakata, H. Enami, and M. Kinoshita, Bull. Chem. Soc. Japan, 55, 3283 (1982).
16. J. G. Buchanan and H. Z. Sable, "Selective Organic Transformations", ed. by B. S. Thyagarajan, Wiley-Interscience, New York (1972), Vol. 2, 1.

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