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SYNTHESIS OF (±)-NOR-STEREPOLIDE

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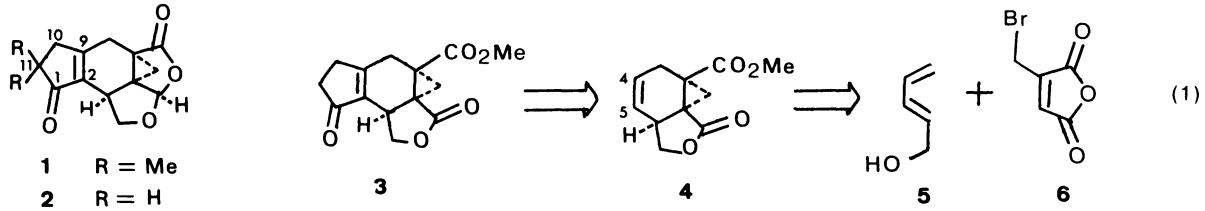
A construction of the pentacyclic framework of sterepolide is described. Stereochemistry of the structure **2** is well established by unequivocal reaction sequences. The Diels-Alder adducts are transformed into a key intermediate **15** by a few steps. Conversion of **15** to **2** is effected by a Nazarov cyclization and subsequent selective reduction of the lactone carbonyl group.

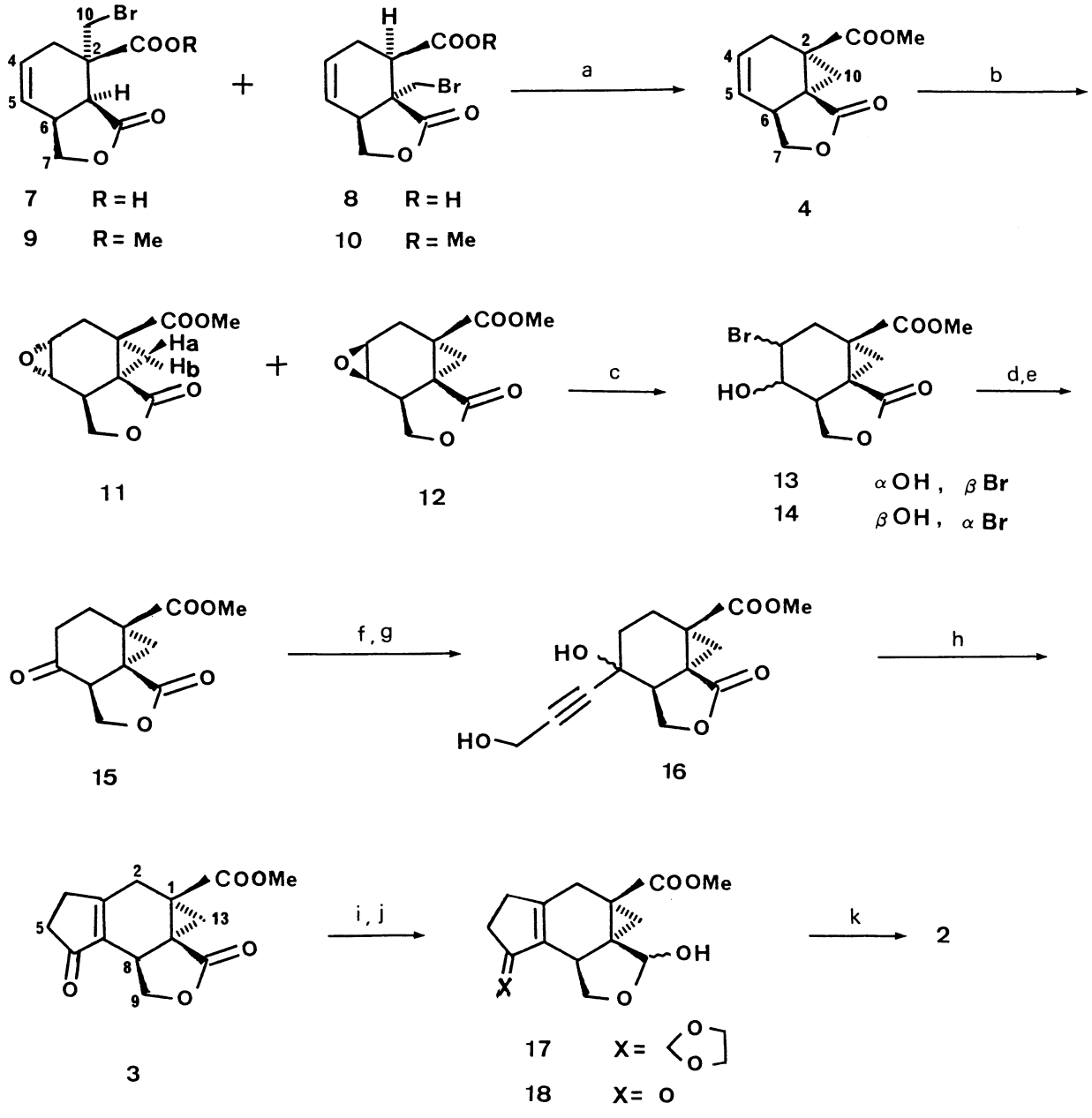
Sterepolide, one of the illudoid-type sesquiterpenes, has been isolated from the fungus Stereum purpureum and the structure **1** was proposed by Ayer and Saeedi-Ghomi.[1] Determination of the structure was mainly based on spectroscopic analyses. Neither X-ray crystallographic analysis nor the chemical conversion has been carried out to confirm the structure. Although the sterepolide skeleton is unique and fascinating , no reports have appeared on the synthetic efforts directed toward the sterepolide framework. Therefore, the unequivocal synthesis of the sterepolide skeleton **2** is of importance from viewpoints of synthetic challenge and of the structural elucidation of **1**.

We wish to report herein a stereocontrolled synthesis of (±)-nor-sterepolide (**2**). The arranged functionality suggests us the retrosynthetic plan illustrated in equation 1. In order to obtain the intermediate **4**, the choice of dienol **5**[2] and anhydride **6**[3] seems most appropriate.[4] Moreover, regiospecific conversion of the resulting olefin **4** to **3** would be accomplished by introduction of a carbonyl group at the C-5 position and subsequent cyclopentenone annulation.



1 R = Me
2 R = H
3 **4** **5** **6** (1)

The Diels-Alder reaction (PhH, rt, 72 h, 72%) of **5** and **6** afforded a mixture of regioisomers **7** and **8** in a ratio of ca. 4.5 : 1, which was treated with diazomethane (MeOH, Et_2O, q.y.) to give a mixture of **9** and **10**.[5] Reaction of the mixture with potassium t-butoxide[6] yielded cyclopropane ester **4**[7] as sole product in 90% yield. The NMR spectrum of **4** showed the cyclopropyl methylene signals at 1.17 and 2.25 ppm (J= 5.5 Hz). Exposure of **4** to m-chloroperbenzoic



a) ^{t}BuOK(1.95 equiv.), ^{t}BuOH, PhH, rt, 1 h; b) 80% MCPBA(2.5 equiv.), Bis(3-^{t}butyl-4-hydroxy-5-methylphenyl) sulfide(cat.), $NaHCO_3$(3 equiv.), $CHCl_3$, reflux, 6 h; c) 48% HBr, $CHCl_3$, 0 °C ⟶ rt, 1 h; d) Jones reagent(ex.), acetone, rt, 6 h; e) Zn, AcOH, rt, 15 h; f) HC≡C-CH_2-OTHP, BuLi, -70 ⟶ -30 °C, 1 h; **15**, -78 °C, 1 h; H_3O^+; g) TsOH, MeOH, rt, 48 h; h) P_2O_5, $MeSO_3H$, rt, 2.5 h; i) ethylene glycol, pyridinium *p*-toluenesulfonate, PhH, reflux, 5 h; j) 0.12 M DIBAL(1 equiv., 1 M=1 mol dm^{-3}) in hexane, THF, -90 °C, 0.5 h; 1 M HCl, rt, 15 min; k) TsOH, PhH, 55 °C, 7 h.

acid(MCPBA) gave epoxides **11** and **12** in 58 and 16% yields, respectively.[8] Stereochemistry of these epoxides was determined on the basis of the works of Paquette[9] and Casadevall.[10] Namely, the α-epoxide **11** revealed the cyclopropyl methylene signals at 2.12(H_a) and 1.46(H_b) ppm in the NMR spectrum, whilst the β-isomer **12** showed the methylene signals at 2.26(H_a) and 0.81(H_b) ppm. The H_b proton of **11** is more deshielded by the oxirane ring than that of **12**. For the construction of a cyclopentenone ring, introduction of a carbonyl group at the C-5 position would be necessary. Both epoxides **11** and **12** were treated with hydrobromic acid to yield fortunately the corresponding bromohydrins **13**(80%) and **14**(70%), respectively.[11] The reasons for the observed selectivity are not obvious. The regioselective cleavage of **11** may reflect the steric influence of the lactone methylene group; the bromonium ion would tend to attack the C-4 position rather than the hindered C-5 position due to the lactone methylene. Jones oxidation of a mixture **13** and **14**, and subsequent reductive removal of bromine provided ketone **15** in good yield.[12] Attention was then focussed on the tetracyclic enone **3**. Since **15** was sensitive to acid and base, conversion of **15** to **3** was troublesome and resulted in the predominant formation of the unwanted cycloheptenone derivative.[13] Of the several ways investigated,[14] the most efficient annulation reaction was the Nazarov cyclization via an acetylenic diol.[15] Thus, reaction of **15** with lithio 3-(2-tetrahydropyranyloxy)propyne followed by acid treatment produced diol **16** as a mixture of stereoisomers in 47% yield from **15**. Next, **16** was converted to **3** with methanesulfonic acid-phosphorous pentoxide in 34% yield.[16] Since the selective reduction of the lactone carbonyl of **3** was unsuccessful, we turned to protection of the enone carbonyl. Acetalization (**17**, 93%) and subsequent reduction with diisobutylaluminium hydride (DIBAL, 1 equiv.) followed by acid workup afforded keto lactol **18** (84%).[17] The final stage has been accomplished by treatment of **18** with p-toluenesulfonic acid (TsOH) to give pentacyclic lactone **2** in 85% yield.[18]

The spectroscopic feature of **2** was in good agreement with that of **1** except for the influences arising from the gem-dimethyl group attached to the C-11 position of the cyclopentenone ring. On the basis of the stereo- and regioselective reaction sequences, the assigned structure of **1** was well confirmed in no doubt.

Attempted introduction of a gem-dimethyl group at the C-11 position of **2** by the use of methyl iodide with a variety of bases (lithium diisopropylamide, lithium hexamethyldisilazide, or potassium t-butoxide) proved unsuccessful and resulted in the destruction of the pentacyclic system. In no case was a substantial amount of isolable product detected. Studies on the synthesis of **1** via other approaches which involve the introduction of a gem-dimethyl group at an earlier stage are in progress.

References

1) W.A. Ayer and M.H. Saeedi-Ghomi, Tetrahedron Lett., 22, 2071 (1981).
2) D. Holland and J.F. Stoddart, J. Chem. Soc., Perkin Trans. 1, 1983, 1553.
3) R.A. Laursen, W.-C. Shen, and K.G. Zahka, J. Med. Chem., 14, 619 (1971).

4) The similar approach was previously employed by Greenlee and Woodward culminated in a novel synthesis of marasmic acid. W. J. Greenlee and R.B. Woodward, Tetrahedron, 36, 3367 (1980).

5) All new compounds have been characterized by 200 MHz NMR, IR, MS spectra, and elemental analyses. The mixture of **7** and **8** was easily separated by chromatography (Mallincrodt CC-4). **7**: mp 200-203 °C, IR ν 3500-2800,1775,1730 cm^{-1}, NMR δ 3.71(d,J=10,10-H,1H), 3.81(dd,J=10,1,10-H,1H), 4.11(dd,J=9,1.5,7-H, 1H), 4.33(dd,J=9,6,7-H,1H), 5.58(d,J=10,5-H,1H), 5.85(dddd,J=10,5.5,3,2,4-H,1H). **8**: mp 180-182 °C, IR ν 3200-2500,1760,1690 cm^{-1}, NMR δ 4.09(ABq,J=10,2H), 4.29(t,J=8,7-H,1H), 4.60(dd,J=8.5,8,7-H,1H), 5.71(d,J=10,5-H,1H), 5.90(m,4-H,1H), MS(m/z) 276, 274(M^+), 258, 256, 105.

6) For a cyclopropanation using potassium t-butoxide as base see: Y. Nakada, R. Endo, S. Muramatsu, J. Ide, and Y. Yura , Bull. Chem. Soc. Jpn., 52, 1511 (1979).

7) **4**: mp 62-64 °C, IR ν 1770,1730 cm^{-1}, NMR δ 1.17(d,J=5.5,10-H,1H), 2.25(d, J=5.5,10-H,1H), 2.51(dm,J=19.5,3-H,1H), 2.99(dddd,J=19.5,3,2,1,3-H,1H), 3.29(m,6-H,1H), 3.72(s,3H), 3.90(dd,J=11,8.5,7-H,1H), 4.65(t, J=8.5, 7-H,1H), 5.62(m,5-H,1H), 5.80(m,4-H,1H), MS(m/z) 208(M^+), 176, 91.

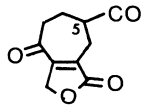
8) **11**: mp 98-100 °C, IR ν 1770,1725 cm^{-1}, NMR δ 1.46(d,J=5.5,10-H,1H), 2.12(d, J=5.5,10-H,1H), 3.21(dd,J=4,1.5,5-H,1H), 3.40(m,4-H,6-H,2H). **12**: mp 130-132 °C, IR ν 1765,1730 cm^{-1}, NMR δ 0.81(d,J=6,10-H,1H), 2.26(d,J=6,10-H,1H), 3.21(m,4-H,5-H,2H), 3.33(m, 6-H,1H), 3.71(s,3H).

9) L.A. Paquette, W.E. Fristad, C.A. Schuman, M.A. Beno, and G.G. Christoph, J. Am. Chem. Soc., 101, 4645 (1979).

10) A. Aumelas, E. Casadevall, and A. Casadevall, Tetrahedron, 34, 2481 (1978).

11) **13**: mp 169-170 °C, IR ν 3500,1760,1730 cm^{-1}, NMR δ 1.26(d,J=6,10-H,1H), 2.17(d,J=6,10-H,1H), 3.70(m, 4-H,5-H,2H), MS(m/z) 306,304(M^+). **14**: mp 121-123 °C, IR ν 3525,1745,1720 cm^{-1}, NMR δ 1.40(d,J=5.5,10-H,1H), 2.28(d, J=5.5,10-H,1H), 3.39(dt,J=9.5,6,6-H,1H), 3.74(ddd,J=9.5,6,4,5-H,1H).

12) **15**: mp 144-146 °C, IR ν 1760, 1730 cm^{-1}, NMR δ 1.61(d, J=5.5, 10-H, 1H), 2.42(d, J=5.5, 10-H, 1H), 2.03(ddd,J=14,9,5, 3-H,1H), 2.35(m,1H), 2.70(m,1H), 3.08(dd,J=9, 6, 6-H,1H), 3.74(s,3H), 4.58(t,J=9, 7-H, 1H), 4.69(dd,J=9,6,7-H,1H), MS(m/z) 224(M^+), 193, 192, 164.

13)  **(i)** By treatment with base or acid, **15** underwent a facile ring-opening reaction leading to the compound **(i)**. **(i)**: mp 108-110 °C IR ν 1760,1730,1665 cm^{-1}, NMR δ 2.05- 2.40(m,2H), 2.90(m,5-H,1H), 3.76(s,3H), 4.91(bs,2H), MS(m/z) 224(M^+).

14) R.M. Jacobson, G.P. Lahm, and J.W. Clader, J. Org. Chem., 45, 395 (1980); L.A. Paquette, W.E. Fristad, D.S. Dime, and T.R. Bailey, ibid., 45, 3017 (1980); T. Hiyama, M. Shinoda, M. Tsukanaka, and H. Nozaki, Bull. Chem. Soc. Jpn., 53, 1010 (1980). Although these approaches were examined, the compound **(i)** was obtained as major product in any case.

15) For a review see: C. Santelli-Rouvier and M. Santelli, Synthesis, 1983, 429.

16) **3**: mp 111 °C, IR ν 1770,1730,1700,1660 cm^{-1}, NMR δ 1.07(d,J=6,13-H,1H), 2.39(d,J=6,13-H,1H), 2.60(m,4-H,5-H,4H), 2.84(dd,J=20,3,2-H,1H), 3.35(d, J=20,2-H,1H), 3.56(ddd,J=10.5,8.5,3,8-H,1H), 3.82(dd,J=10.5,8.5,9-H,1H), 3.74(s,3H), 4.88(t,J=8.5, 9-H,1H), MS(m/z) 262(M^+),231,159.

17) **18**: IR ν 3400,1715,1695,1655 cm^{-1}, NMR δ 0.93(d,J=5.5,1H), 1.98,2.00(d,J=5.5, stereoisomeric,1H), 2.4-3.8(m,9H), 4.56,4.60(t,J=8,stereoisomeric,1H), 4.96, 5.28(s,stereoisomeric,1H), MS(m/z) 264(M^+), 246, 232, 224, 128.

18) **2**: mp 129-130 °C, IR ν 1772,1701,1645 cm^{-1}, NMR δ 1.37(d,J=6,1H), 1.81(d,J=6,1H), 2.50(m,4H), 2.99(ABq,J=21,2H), 3.50(dd,J=8,7.5,1H), 3.61(dd,J=7.5,7,1H), 4.54(dd,J=8,7,1H), 5.72(s,1H), MS(m/z) 232(M^+),202,174.

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