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SYNTHESIS OF (+)-BAIYUNOL, THE DITERPENE AGLYCONE OF THE SWEET GLYCOSIDE BAIYUNOSIDE†

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Abstract -- A chiral synthesis of (+)-baiyunol, the labdane-type diterpene aglycone of the sweet glycoside baiyunoside, was achieved starting from (S)-3-hydroxy-2,2-dimethylcyclohexanone.

In 1983 Tanaka and his co-workers reported the isolation of a new glycoside named baiyunoside from a Chinese plant drug, "Bai-Yun-Shen" (roots of Phlomis betonicoides Diels).[1,2] Its aglycone named (+)-baiyunol was obtained as acid-unstable crystals and shown to have the structure **1** belonging to the labdane family of diterpenes.[1,2] Baiyunoside **2** was about 500-fold sweeter than sucrose and assigned the structure **2**. Our continuing interest in the synthesis of natural sweetner itself (hernandulcin[3]) or its terpene aglycone part (steviol[4]) prompted us to undertake a chiral synthesis of (+)-baiyunol **1**, although a synthesis of (±)-**1** had already been reported by Nishizawa et al.[5]

Our synthesis as shown in the Scheme employed (S)-3-hydroxy-2,2-dimethylcyclohexanone **3** as the starting material. The ketol **3** (98.4 % e.e.) was readily available by the microbial reduction of 2,2-dimethylcyclohexane-1,3-dione,[6] and has been utilized by us in the chiral syntheses of various terpenes.[7] In our recent synthesis of (-)-K-76, a complement inhibitor, we employed a bicyclic hydroxy ester **4a** as an intermediate.[8] The ester **4a** was synthesized from **3** in 13 steps in 6.2 % overall yield. Our plan was to convert **4a** to bromide **8**, whose coupling with p-tolyl-3-furfuryl sulfone would generate the carbon skeleton of the target molecule as shown in **9**.

Over two decades ago van Tamelen et al. developed the benzylation-isomerization protocol for the conversion of (±)-**4a** to (±)-**6**.[9] The first step of our synthesis was therefore benzylation of **4a** with benzyl chloride (BnCl) and NaH in DMF. Chromatographic purification of the product gave a benzyloxy β,γ-unsaturated ester (νmax 1735 cm^{-1}) in 48 % yield as the major product. This was thought to be **5** with an α-oriented CO_2Me group on the basis of its ^1H NMR spectrum in which a singlet was

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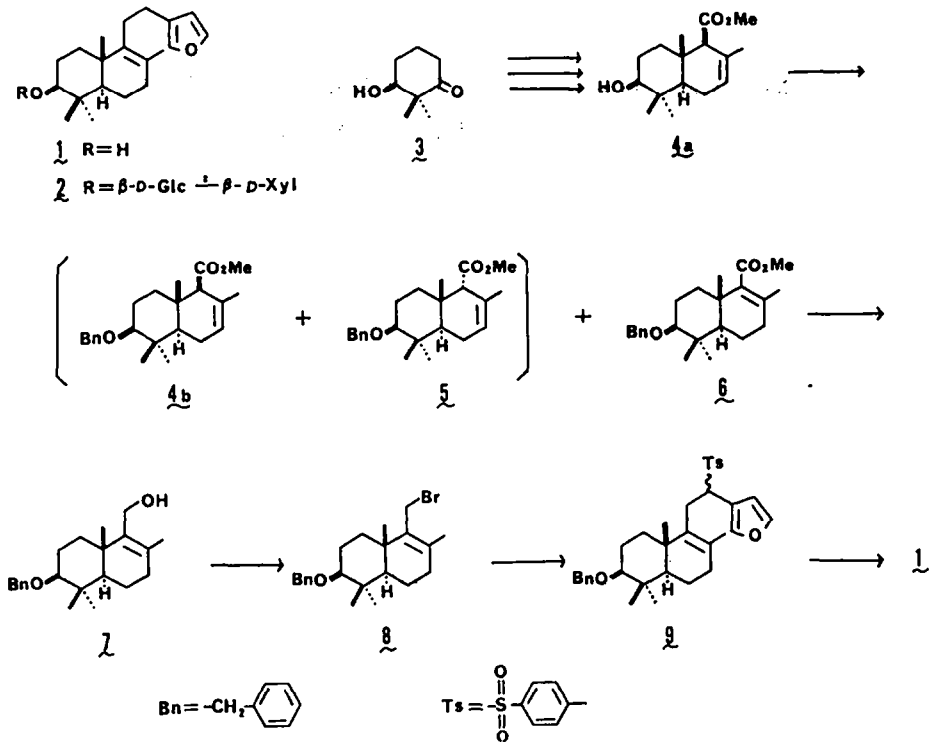

found at δ 2.51 ($CHCO_2Me$). The starting **4a** and related compounds with a β-oriented CO_2Me group showed the corresponding singlet due to $CHCO_2Me$ at δ 2.8-3.0.[8] The minor product obtained in 23 % yield was the desired α,β-unsaturated ester **6** [νmax 1725 (s), 1660 (w) cm^{-1}] contaminated with a small amount (6-7 %) of **4b** as judged from its ^1H NMR spectrum with a very small signal at δ 5.60 due to the olefinic proton of **4b**. The mixture of **6** and **4b** was unfortunately inseparable even by GLC or TLC. The β,γ-unsaturated ester **5** could again be equilibrated with NaH in DMF to give a mixture of **5** and **6** contaminated with a small amount of **4b** in a ratio of 60:37 as analyzed by GLC. After chromatographic separation to secure the desired **6**, the recovered **5** was recycled to give an additional amount of **6**.

Reduction of **6** with LAH gave **7** in 79 % yield, which was purified by recrystallization. Subsequent reaction of **7** with methanesulfonyl chloride (MsCl) in the presence of Et_3N in CH_2Cl_2 yielded a mesylate, which was immediately treated with LiBr to give bromide **8**. Alkylation of p-tolyl 3-furylmethyl sulfone with **8** was effected with n-BuLi in THF-HMPA as the base furnishing the coupling product **9** in 65 % yield from **7**. Finally reduction of **9** with Li in liq NH_3-THF at -78° for 15 min removed both the p-tolylsulfonyl and the benzyl group to give **1** in 52 % yield. After recrystallization, the synthetic (+)-baiyunol **1**, m.p. 85.5-87.0°, $[\alpha]_D^{22}$ +78.8° ($CHCl_3$) [lit.[1,2] m.p. 85.5-86°; $[\alpha]_D^{21}$ +64.0° ($CHCl_3$)], showed spectral data (IR, ^1H NMR and ^{13}C NMR) identical to those of the natural (+)-**1**. Fortunately, our final product **1** was completely pure without any detectable contamination with the double bond isomer resulting from **4b**. Since the bromide resulting from **4b** was a homoallylic bromide unlike the allylic bromide **8**, only **8** must have reacted with the sulfone carbanion because of the lower reactivity of the homoallylic bromide compared with

that of **8**.

In conclusion, the first chiral synthesis of (+)-baiyunol was achieved in 12.0 % overall yield in 5 steps from **4a**, or in 0.7 % overall yield in 18 steps from **3**. The present synthesis opened the way to achieve a chiral synthesis of baiyunoside **2** itself.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra were measured on a Jasco IRA-102 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 100 MHz on a Jeol JNM FX-100 spectrometer. ^{13}C NMR spectra were measured with TMS as an internal standard at 25 MHz on a Jeol JNM FX-100 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Merck Kieselgel 60 (particle size 0.063-0.200 mm) used for SiO_2 column chromatography unless otherwise stated. GLC analyses were performed on a Hitach 163 gas chromatograph.

Methyl (1R,4aR,6S,8aS)-1,4,4a,5,6,7,8,8a-octahydro-6-benzyloxy-2,5,5,8a-tetramethylnaphthalene-1-carboxylate **5** and methyl (4aR,6S,8aS)-3,4,4a,5,6,7,8,8a-octahydro-6-benzyloxy-2,5,5,8a-tetramethylnaphtnalene-1-carboxylate **6**. To a stirred soln of **4a** (450 mg, 1.69 mmol) in dry and deoxygenated DMF (5 ml) was added NaH (80 mg, 60 % mineral oil despersion, 2 mmol) at room temp under Ar. The stirring was continued for 1 h at 40° and then benzyl chloride (0.214 ml, 1.87 mmol) was added to the pale orange suspension. The mixture was stirred for 2 h at 40° and then poured into ice-water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Art. 9385, 30 g). Elution with *n*-hexane-ether (50:1-25:1) gave 287 mg (47.7 %) of **5** in earlier fractions and 140 mg (23.2 %) of **6** in later fractions. To a stirred soln of **5** (287 mg) in dry and deoxygenated DMF (5 ml) was added NaH (35 mg) at room temp, and the mixture was stirred for 3 h at 60° under Ar. The mixture was poured into ice-water and extracted with ether. GLC (column OV-17 at 205°, 1 m x 4 mm; carrier gas N_2, 0.9 kg/cm^2) analysis of the mixture indicated the presence of 60.5 % of **5** (Rt 8.7 min) and 37.8 % of **6** (Rt 12.7 min, a small amount of **4b** could not be separated). Separation by SiO_2 chromatography gave 170 mg (59.2 %) of **5** and 54 mg (18.8 %) of **6**. The recovered **5** (170 mg) was isomerized to give 52 mg (30.6 %) of **6** and 106 mg (62.3 %) of **5**. The amount of **4b** contained in **6** could not be decided by GLC. **6** was used in the next step without further purification. **5**: νmax (film) 1735 (s), 1500 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 0.94 (3H, s), 0.97 (3H, s), 1.05 (3H, s), 1.63 (3H, br.s), 1.20-2.10 (7H, m), 2.51 (1H, br.s), 2.95 (1H, m), 3.68 (3H, s), 4.45 (1H, d, J=12 Hz), 4.65 (1H, d, J=12 Hz), 5.66 (1H, m), 7.40 (5H, s). **6**: νmax (film) 1725 (s), 1660 (w), 1500 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 0.87 (3H, s), 0.99 (3H, s), 1.20 (3H, s), 1.60 (3H, s), 1.10-2.20 (9H, m), 2.92 (1H, m), 3.72 (3H, s), 4.45 (1H, d, J=12 Hz), 4.65 (1H, d, J=12 Hz), 7.42 (5H, s).

(4aR,6S,8aS)-(+)-3,4,4a,5,6,7,8,8a-Octahydro-6-benzyloxy-1-hydroxymethyl-2,5,5,8a-tetramethylnaphthalene **7**. To a stirred and ice-cooled suspension of LAH (40 mg, 1.05 mmol) in dry ether (20 ml) was added dropwise a soln of **6** (220 mg, 0.618 mmol) in dry ether (10 ml) and the stirring was continued for 4 h at room temp. Sat Na_2SO_4 aq soln was added dropwise to the mixture at 0°. After drying ($MgSO_4$), the mixture was filtered and the filter-cake was washed with ether. The combined ether solns were concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Art. 9385, 10 g). Elution with *n*-hexane-ether (4:1) gave 55 mg of **6** in earlier fractions and 120 mg (59 %, 79 % based on consumed **6**) of **7** in later fractions. A portion of **7** was recrystallized from *n*-pentane to give pure **7** as colorless needles, m.p. 89-90°; $[\alpha]_D^{23.5}$ +114° (c=0.440, $CHCl_3$); νmax (KBr) 3360 (s), 1495 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.89 (3H, s), 0.99 (3H, s), 1.01 (3H, s), 1.73 (3H, s), 1.10-2.20 (10H, m), 3.45 (1H, dd, J=4, 10 Hz), 4.04 (1H, d, J=12 Hz), 4.22 (1H, d, J=12 Hz), 4.46 (1H, d, J=12 Hz), 4.67 (1H, d, J=12 Hz), 7.34 (5H, m). (Found: C, 80.42; H, 9.59. Calc for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82 %).

(4aR,6S,8aS)-3,4,4a,5,6,7,8,8a-Octahydro-6-benzyloxy-1-[2-(3-furyl)-2-p-tosylethyl]-2,5,5,8a-tetramethylnaphthalene **9**.

i) MsCl (0.06 ml, 0.78 mmol) was added dropwise to a cooled soln of 7 (135 mg, 0.41 mmol) and Et_3N (0.13 ml, 0.93 mmol) in CH_2Cl_2 (5 ml) at -60° under Ar. The resulting white suspension was stirred for 30 min and then treated with a soln of LiBr (125 mg, 1.44 mmol) in dry THF (1.5 ml). The mixture was warmed slowly to -20° and stirred for 45 min. At the end of this period, the mixture was poured into water and extracted with n-pentane. The n-pentane soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 160 mg (quantitative) of crude 8. This unstable colorless oil 8 was used immediately in the next step without further purification.

ii) To a stirred and cooled soln of p-tolyl 3-furylmethyl sulfone (125 mg, 0.530 mmol) in dry THF (3 ml) and HMPA (0.8 ml) was added dropwise a soln of n-BuLi (1.5 N in n-hexane, 0.35 ml, 0.53 mmol) at -78° under Ar and the resulting yellow soln was stirred for 20 min. A soln of 8 (160 mg) in dry THF (1.5 ml) was added dropwise to the mixture. The mixture was stirred for 1.5 h at the same temp, poured into sat NH_4Cl aq soln and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (10 g). Elution with n-hexane-ether (8:1) gave 147 mg (65 %) of 9 as a white amorphous solid, νmax ($CHCl_3$) 1600 (m), 1500 (m), 1315 (s), 1305 (s), 1150 (s), 1090 (s) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.78, 0.82, 0.94, 0.99 (total 9H, each s), 1.10-2.20 (12H, m), 2.40 (3H, s), 2.56-3.35 (3H, m), 3.95-4.28 (1H, m), 4.41, 4.45, 4.64, 4.68, (total 2H, each d, J=12 Hz), 6.50, 6.55 (total 1H, each m), 6.98-7.65 (6H, m). This was employed in the next step without further purification.]

(+)-Baiyunol 1. To a stirred and cooled soln of 9 (142 mg, 0.26 mmol) in liq NH_3 (15 ml) and dry THF (5 ml) was added Li (30 mg, 4.3 mmol) at -78°. After 15 min, solid NH_4Cl (2 g) was added to the dark blue mixture. The resulting white suspension was diluted with ether and NH_3 was removed at room temp. The ether soln was filtered and the filter-cake was washed with ether. The ether soln was concentrated in vacuo. The residue was chromatographed over SiO_2 (10 g). Elution with n-hexane-ether (4:1) gave 41 mg (52 %) of 1 as a white solid. Recrystallization of 1 from n-hexane gave pure 1 as colorless needles, m.p. 85.5-87.0° (lit.[1,2] m.p. 85.5-86.0°); $[\alpha]_D^{22}$ +78.8° (c=0.655, $CHCl_3$) [lit.[1,2] $[\alpha]_D^{21}$ +64.0° (c=1.47, $CHCl_3$)]; νmax (KBr) 3340 (s), 3025 (m), 2990 (s), 2960 (s), 2900 (s), 2850 (s), 2740 (w), 1625 (w), 1560 (w), 1505 (m), 1470 (m), 1445 (m), 1435 (m), 1390 (m), 1380 (m), 1360 (w), 1340 (w), 1300 (w), 1260 (w), 1215 (w), 1195 (w), 1160 (m), 1140 (w), 1120 (w), 1100 (m), 1090 (w), 1070 (m), 1060 (m), 1050 (s), 1030 (s), 1010 (m), 990 (m), 970 (w), 950 (w), 935 (w), 910 (w), 880(s), 850 (w), 800 (w), 780 (m), 725 (m), 695 (w) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.83 (3H, s), 0.98 (3H, s), 1.03 (3H, s), 1.62 (3H, s), 1.05-2.55 (15H, m), 3.25 (1H, m), 6.30 (1H, dd, J=0.8, 1.8 Hz), 7.24 (1H, dd, J=0.8, 1.8 Hz), 7.36 (1H, t, J=1.8 Hz); ^{13}C NMR (25 MHz, C_5D_5N) δ 16.4, 19.1, 19.5, 20.3, 26.0, 28.6 (2C), 29.2, 34.0, 35.5, 39.1, 39.4, 51.4, 78.1, 111.4, 126.1, 126.6, 139.1, 140.1, 143.3. In their paper Tanaka et al. erroneously stated the signal at δ 29.2 to be due to 2 carbons.[1,2] However, the signal at δ 28.6 was due to 2 carbons. (Found: C, 79.04; H, 9.90. Calc for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00 %).

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REFERENCES

1 T. Tanaka, O. Tanaka, Z.-W. Lin, J. Zhou and H. Ageta, Chem. Pharm. Bull. 31, 780 (1983).
2 T. Tanaka, O. Tanaka, Z.-W. Lin and J. Zhou, Chem. Pharm. Bull. 33, 4275 (1985).
3 K. Mori and M. Kato, Tetrahedron 42, 5895 (1986).
4 K. Mori, Y. Nakahara and M. Matsui, Tetrahedron 28, 3217 (1972).
5 M. Nishizawa, H. Yamada and Y. Hayashi, Tetrahedron Lett 27, 3255 (1986).
6 K. Mori and H. Mori, Tetrahedron 41, 5487 (1985).
7 K. Mori and H. Mori, Tetrahedron 42, 5531 (1986).
8 K. Mori and M. Komatsu, Liebigs Ann. Chem. submitted for publication.
9 E. E. van Tamelen, M. A. Schwartz, E. J. Hessler and A. Storni, Chem. Commun. 409 (1966).