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Stereoselective synthesis of (2*R*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethylheptanoic acid and determination of the absolute stereochemistry of the natural product from callipeltin A

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Abstract—A revised stereostructure of 3-hydroxy-2,4,6-trimethylheptanoic acid, the β-hydroxy acid that acylates the N-terminus of callipeltin A, is proposed on the basis of analysis of *J*-coupling in the ^{1}H NMR spectrum of the acetonide derivative obtained from the acid hydrolysate of callipeltin A. The proposed structure was definitively confirmed by enantioselective synthesis.

Recently, we reported the synthesis of (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid, the proposed β-hydroxy acid unit that acylates the N-terminus of callipeltin A **1**.[1] However, we found that its ^{1}H NMR spectral data were not identical with those of the corresponding unit obtained from the acid hydrolysate of callipeltin A **1**, thus indicating that the absolute configuration of the aforementioned natural unit should be revised. Because the (3*R*)-stereochemistry at the carbinol centre was unambiguously established by a modified Mosher's method,[2] the stereochemical revision should concern the C(2) stereogenic centre, the C(4) stereogenic centre, or both.

In order to gain more insights into the stereochemistry of the natural β-hydroxy acid unit, we subjected a 40 mg sample of callipeltin A **1** to acid hydrolysis followed by dichloromethane extraction, to obtain 4.0 mg of the natural β-hydroxy acid **2**. This latter was readily transformed in the 1,3-*O*-isopropylidene derivative **4** by the three steps sequence depicted in the Scheme 1. The vicinal coupling constant for H2/H3 (8.2 Hz) was indicative of an *anti*-relationship between these two protons.[3] Thus, the (2*R*,3*R*) configuration was firmly established.

From these results we reached the conclusion that the correct stereochemistry of the natural β-hydroxy acid **2** must be (2*R*,3*R*,4*R*). This revised stereochemistry has been confirmed by enantioselective synthesis as described herein.

Our planned synthetic route to the above fragment **2**, outlined in Scheme 2, is similar to that used for the synthesis of (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid.[1] Indeed we elaborated a flexible synthetic strategy which was amenable to the construction of the different stereoisomers of the β-hydroxy acid unit in **1**.

In this case Brown's crotylboration[4] was selected as the key step for the assembly of the C3–C4 *anti*-propionate unit in β-hydroxy acid **2**. Thus, aldehyde **8**, obtained in high yield (three steps, 87%) from commercially available methyl (2*S*)-2-methyl-3-hydroxy propionate **5**, was reacted with the allyl borane derived from (+)-*B*-methoxydiisopinocampheyl borane and (*E*)-butene to give the *anti*-homoallylic alcohol **9**. The diastereomeric purity of **9** was >98% as judged by the NMR spectra of the crude reaction mixture. We encountered difficulties in separating **9** in acceptable yield from the isopinocampheol arising from the reaction. Thus, crude **9** was converted into the TBS-protected derivative **10** which was easily separated from the protected isopinocam-

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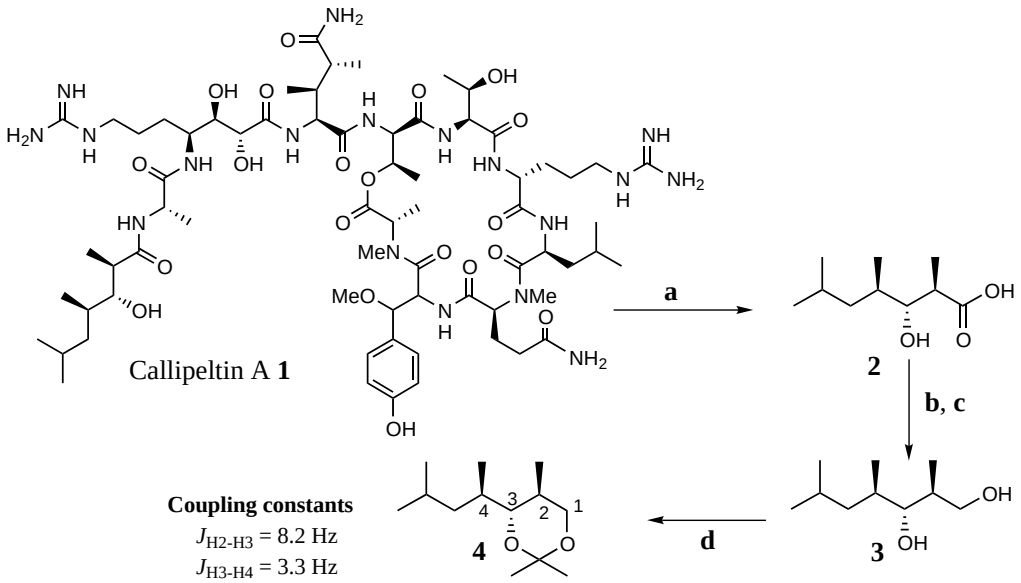
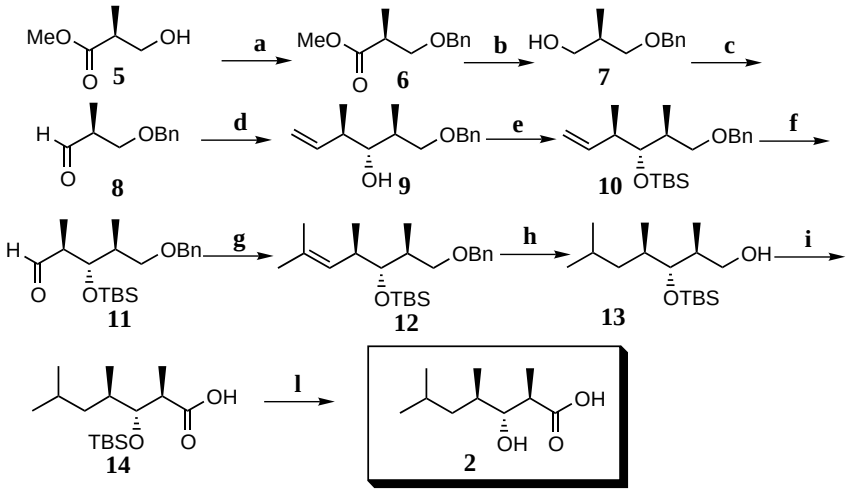


Scheme 1. *Reagents and conditions*: (a) HCl 6N, 130°C, 6 h, then CH_2Cl_2 extraction; (b) CH_2N_2, rt, quantitative; (c) $LiBH_4$, dry MeOH, 2 h, 96%; (d) dimethoxypropane dry, *p*-TsOH (cat.), quantitative.



Scheme 2. *Reagents and conditions*: (a) BTCA, TfOH, 0°C to rt, 3 h, 94%; (b) $LiBH_4$, dry MeOH, 2 h, 96%; (c) DMSO, $(COCl_2)$, −78°C, 30 min, then **7**, Et_3N, −78°C to rt, 1 h, 97%; (d) *t*-BuOK, (*E*)-but-2-ene, *n*-BuLi, −78 to −45°C, (+)-*B*-methoxydiisopinocampheylborane, $BF_3{\cdot}OEt_2$, aldehyde **8**, −78°C, 4 h; (e) 2,6-lutidine, TBSOTf, 0°C to rt, 2 h, 76%, two steps; (f) OsO_4/*N*-methylmorfoline-*N*-oxide, rt, 12 h, then H_5IO_6 15 min, 97%; (g) isopropyltriphenylphosphonium iodide, *n*-BuLi, rt 3 h, 84%; (h) H_2/$Pd(OH)_2$, 3 atm, 2 days, 90%; (i) $NaIO_4$/$RuCl_3{\cdot}H_2O$ (cat.), 97%; (l) MeOH/HCl, 25°C, 3 h, quantitative.

pheol by silica gel chromatography (76% yield of **10** from **8**).[5] Oxidative cleavage of the terminal double bound (OsO_4, NMO, acetone–water, H_5IO_6) led to the aldehyde **11**. This latter was subjected to the same reaction sequence previously developed by us for the synthesis of (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid.[1] Thus, Wittig olefination followed by one-pot reduction of the alkene bond and removal of the benzyl protecting group, afforded alcohol **13** which was smoothly oxidised to the protected β-hydroxy acid **14**.

The complete overlap of the NMR data of the synthetic derivative **2**,[6] obtained by acid hydrolysis of **14** (MeOH/HCl), with that of the corresponding natural unit **2**, unambiguously defined the (2*R*,3*R*,4*R*)-configuration. Further confirmation of the absolute stereochemistry of natural **2** was obtained from comparison of specific rotation data (synthetic **2**: $[\alpha]_D = +14.9$, (*c* 0.4), $CHCl_3$; natural **2**: $[\alpha]_D = +14.4$, (*c* 0.4, $CHCl_3$).

In conclusion, the stereochemistry of the β-hydroxy acid unit that acylates the N-terminus of the cyclodepsipeptide callipeltin A **1** was definitively established by asymmetric synthesis. Furthermore, our synthesis of the protected β-hydroxy acid **14** is short (nine steps from the commercially available L-malate dimethyl ester **5**), efficient (47% overall yield) and amenable to scale-up.

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References

1. Zampella, A.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2002**, *13*, 681–685.
2. Zampella, A.; D'Auria, M. V.; Gomez-Paloma, L.; Casapullo, A.; Minale, L.; Debitus, C.; Henin, Y. *J. Am. Chem. Soc*. **1996**, *118*, 6202–6209.
3. ^{1}H NMR ($CDCl_3$, 500 MHz) for compound **4**, δ: 4.22 (1H, dd, $J=10.3$, 5.1 Hz, H-1a), 3.75 (1H, dd, $J=10.3$, 2.7 Hz, H-1b), 3.40 (1H, dd, $J=8.2$, 3.3 Hz, H-3), 1.62 (1H, m, H-4), 1.60 (2H, m's, H-2, H-6), 1.30/1.32 (6H, s's, acetonide Me), 1.20 (1H, m, H-5a), 1.13 (1H, m, H-5b), 0.94 (3H, d, $J=6.6$ Hz, Me-8), 0.90 (3H, d, $J=6.6$ Hz, Me-9), 0.86 (3H, d, $J=6.6$ Hz, Me-10), 0.84 (3H, d, $J=6.6$ Hz, Me-7).
4. Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem*. **1989**, *54*, 1570–1576.
5. NMR data ($CDCl_3$, 500 MHz) and specific rotation (chloroform) for compound **10**. ^{1}H NMR δ: 7.34 (5H, m, *benzyl*), 5.95 (1H, m, H-5), 5.03 (1H, d, $J=5.2$, H-6a), 5.0 (1H, s, H-6b), 4.50 (2H, s, benzylic CH_2), 3.60 (2H, m, H-1a, H-3), 3.40 (1H, t, $J=8.8$ Hz, H-1b), 2.41 (1H, m, H-4), 2.01 (1H, m, H-2) 1.08 (3H, d, $J=6.6$ Hz, Me-4), 1.02 (3H, d, $J=6.6$ Hz, Me-2), 0.95 (9H, s, Si-C(CH_3)$_3$, 0.1 (3H, s, Si-(CH_3)), 0.12 (3H, s, Si-(CH_3); ^{13}C NMR δ: 141.3, 138.8, 128.3, 127.6, 127.4, 115.1, 79.6, 77.8, 73.0, 72.9, 42.0, 38.2, 26.1, 18.4, 18.2, 14.9, −3.8, −4.0; $[\alpha]_D=-4.3$ (*c* 2.2, $CHCl_3$).
6. NMR data ($CDCl_3$, 500 MHz) and specific rotation (chloroform) for synthetic **2**. ^{1}H NMR δ: 3.48 (1H, dd, $J=7.7$, 4.1 Hz, H-3), 2.73 (1H, q, $J=7.7$ Hz, H-2), 1.70 (1H, m, H-4), 1.64 (1H, m, H-6), 1.26 (3H, d, $J=7.7$ Hz, Me-2), 1.18 (1H, m, H-5a), 1.12 (1H, m, H-5b), 0.96 (3H, d, $J=5.8$ Hz, Me-6), 0.92 (3H, d, $J=6.8$ Hz, Me-6), 0.84 (3H, d, $J=6.8$ Hz, Me-4); ^{13}C NMR δ: 180.7, 78.2, 42.1, 39.4, 33.4, 25.2, 24.2, 21.2, 16.6, 14.6.; $[\alpha]_D=+14.9$ (*c* 0.4, $CHCl_3$).