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First total synthesis of theopederin B

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ABSTRACT

Total synthesis of theopederin B, isolated from marine sponge, was accomplished by coupling pederic acid, as the left half, with trioxodecaline amine as the right half. Key reactions for synthesizing the amine were SmI_2-promoted Reformatsky reaction, stereoselective allylation followed by Sharpless asymmetric epoxidation for construction of the functionalized side chain, and 1,3-dioxane ring construction followed by azide insertion.

Mycalamides,[1] onnamides,[2] and theopederins[3] have been isolated from marine sponges, and their structures (e.g., mycalamide A (**1**), theopederins B (**2**) and D (**3**); Fig. 1) strikingly resemble that of pederin,[4] a potent insect toxin isolated from *Pederus fuscipes*. These marine natural products contain an identical pederic acid unit as the left half, and have the amino-trioxadecaline ring with slightly different side chains as the right half. They exhibit potent antitumor, antiviral, and immunosuppressive activities. Their unique structures and potent biological activities have attracted the attention of numerous synthetic chemists; total syntheses have been reported for pederin,[5–9] mycalamides A[10–15] and B,[10,16] onnamide A,[17] and theopederin D (**3**).[18,19] We now report the first total synthesis of theopederin B (**2**), which was isolated from marine sponges of the genus *Theonella*. It is markedly cytotoxic against P388 murine leukemia cells (IC_{50} 0.1 ng/mL) and shows promising antitumor activity ($T/C = 173$) against P388 (ip).[3] The right half has a methyl 5-hydroxy-6-hexanoyl moiety as the side chain.

Our synthetic strategy is outlined in Scheme 1. Synthesis of theopederin B (**2**) would be accomplished by coupling of pederic acid **i** with amine **ii**. We have already reported an efficient synthesis of the left half, **i**.[20] The right half, **ii**, would be synthesized via SmI_2-promoted intramolecular Reformatsky reaction[21] for construction of δ-lactone **v** having an axial alcohol, followed by introduction of the side chain, then insertion of the hydroxyl group (**v**→**iv**→**iii**), and construction of 1,3-dioxan-4-amine ring (**iii**→**ii**).

The synthesis of the right half started with commercially available D-arabitol (**4**) (Scheme 2). The Wittig reaction of aldehyde **5**,[22] prepared from **4**, with $Ph_3P^+MeBr^-$ and NaHMDS afforded olefin **6** (49% overall yield from **4**), which was acylated with $Me_2CBrCOBr$ to give bromoacetate **7** in 90% yield. After ozonolysis of **7**, treatment of the resulting aldehyde **8** with SmI_2 in THF resulted in intramolecular Reformatsky reaction to give δ-lactone **9**[23] in 88% yield (2 steps) as a single product, which has the desired α-axial alcohol. The configuration was supported by the coupling constant ($J = 3.4$ Hz) between 12-H and 13-H. Methylation of the alcohol in **9** was performed by treatment with NaH and MeI in DMF or *t*-BuOK and MeI in THF to give the methyl ether **10** in 96% or 91% yield, respectively.[24] Reduction of the lactone **10** with DIBAH, followed by acetylation afforded acetate **11** in 90% yield (2 steps). Treatment of **11** with allylTMS in the presence of TMSOTf in CH_2Cl_2 at 0 °C effected stereoselective allylation[25] to give **12**[26] in 80% yield. NOE measurements and the coupling constant between 12-H and 13-H in **12** ($J = 2.0$ Hz) support the conformation **12A** having α-axial allyl group (Fig. 2).

Next, introduction of a hydroxyl group at C-17 in the side chain and construction of the 4-amino-1,3-dioxane ring were accomplished (Scheme 3). Treatment of the benzylidene **12** with DIBAH resulted in regioselective reductive ring-opening to give alcohol-benzylether **13**[27] in 93% yield. At this stage, the conformation of the tetrahydropyran ring **13** is different from that of **12**. NOE measurements and the coupling constant between 12-H and 13-H in **13** ($J = 9.5$ Hz) support the conformation of **13A** (Fig. 2). After Swern oxidation of the alcohol **13**, acetalization with CSA and $CH(OMe)_3$ in MeOH afforded dimethylacetal **14** in 97% yield (2 steps). Elongation of the side chain was performed by ozonolysis of the olefin in **14** and subsequent Horner–Wadsworth–Emmons (HWE) reaction using $(EtO)_2P(O)CH_2CO_2Et$ to give α,β-unsaturated ester **15** in 92% yield (2 steps). After DIBAH reduction of **15**, Sharpless asymmetric epoxidation[28] of **16** with (+)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, and *t*-BuOOH afforded β-epoxide **17** in 88% yield. The Swern oxidation of **17** followed by HWE

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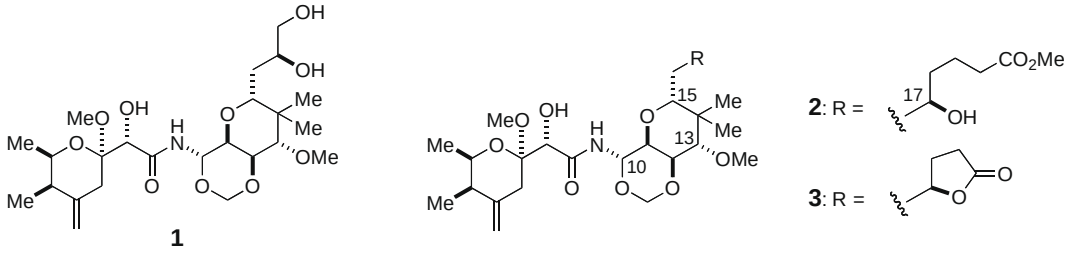
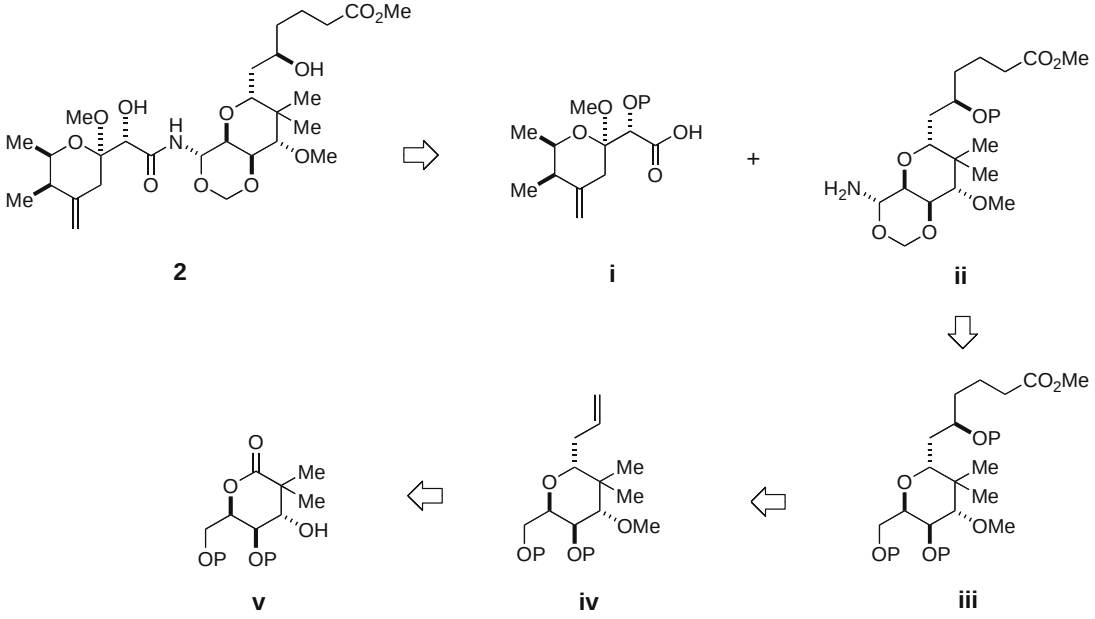
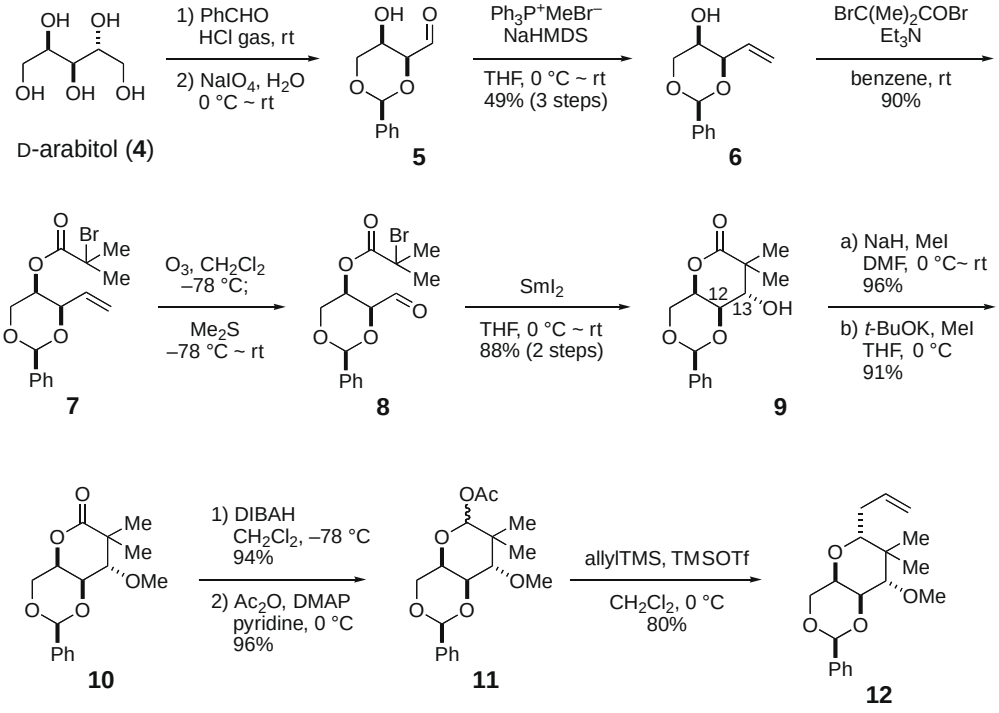


Figure 1. Structures of mycalamide A (**1**), theopederins B (**2**) and D (**3**).



Scheme 1. Synthetic plan for theopederin B (**2**).



Scheme 2.

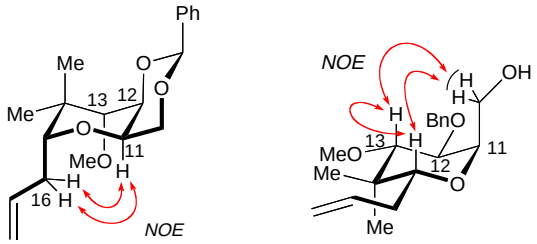
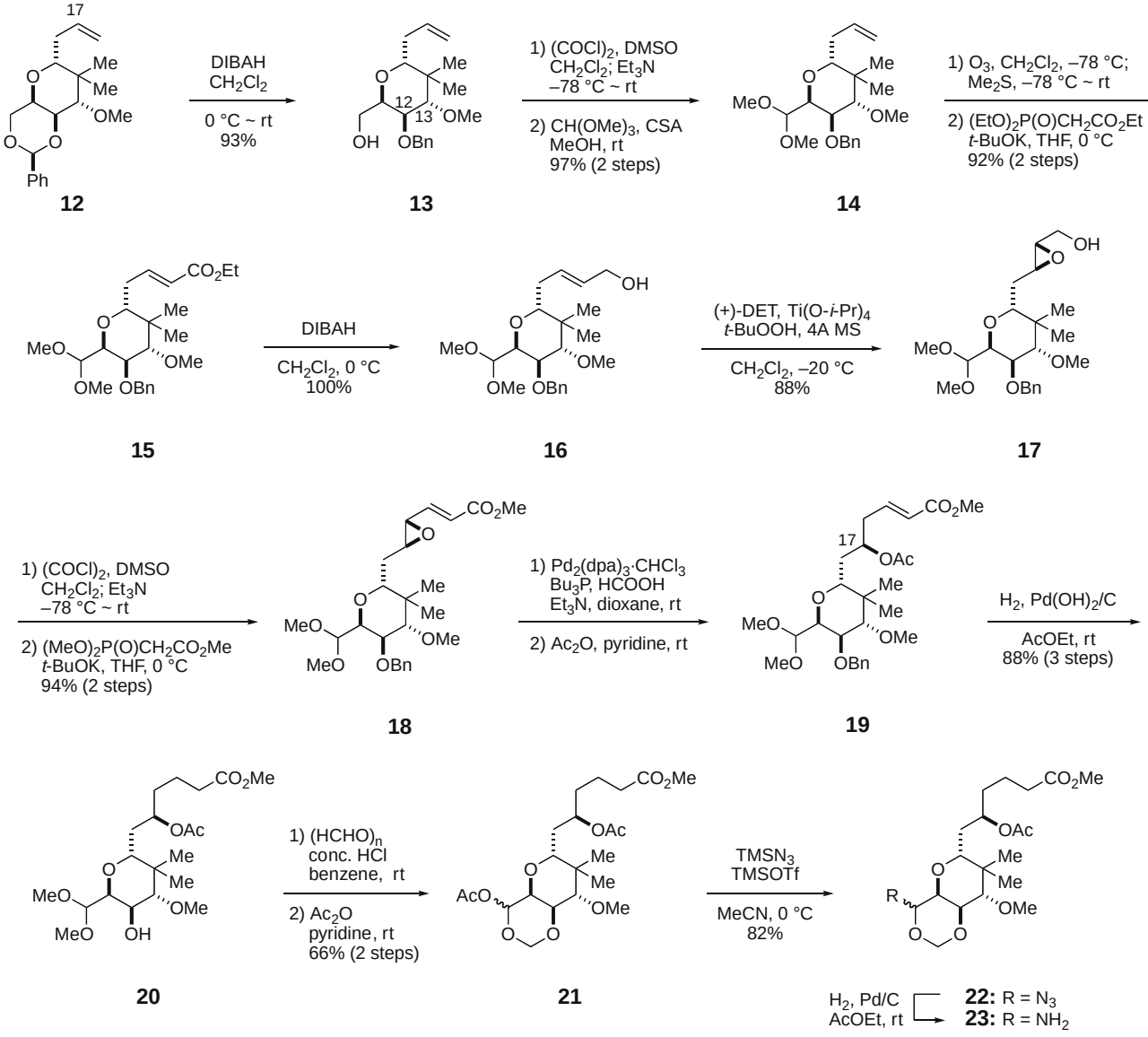


Figure 2. Conformations of **12** and **13**, and observed NOEs.

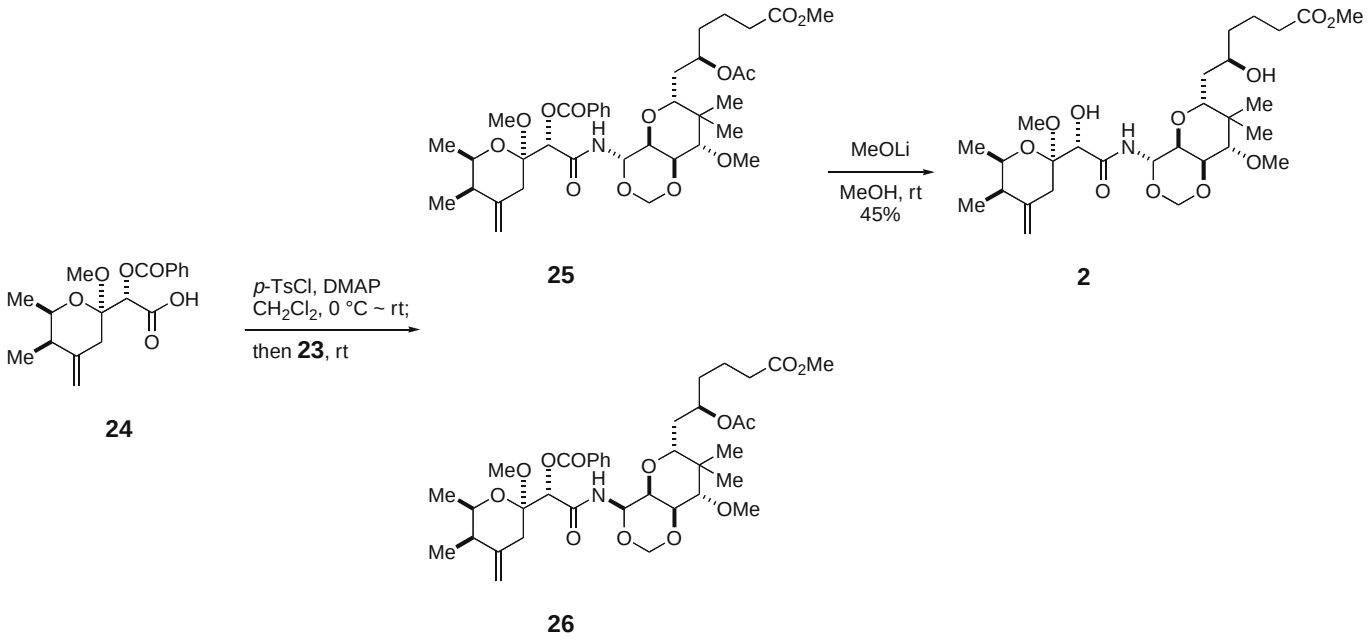
reaction gave α,β-unsaturated ester **18** in 94% yield. Regioselective epoxide ring-opening by palladium-catalyzed reduction[29] of **18** with HCOOH and subsequent acetylation afforded α,β-unsaturated ester **19**, hydrogenation of which, accompanied with removal of the benzyl group, gave alcohol **20**[30] in 88% yield (3 steps). Treatment of the acetal-alcohol **20** with paraformaldehyde and concd HCl followed by acetylation provided 1,3-dioxane acetal **21** in 66% yield (2 steps). Treatment of the acetal **21** with $TMSN_3$ and TMSOTf in MeCN gave a 2:1 mixture of α- and β-azides **22**[31] in 82% yield. Hydrogenation of **22** on Pd/C afforded the right half amine **23**.[32]

For coupling of the left and right halves, **24** and **23**, we employed Kishi's conditions[10] (Scheme 4). Treatment of the carboxylic acid **24** with *p*-TsCl and DMAP followed by addition of the amine **23** produced α-amide **25** and β-amide **26** in 30% and 11% yields, respectively. Methanolysis of **25** with MeOLi in MeOH furnished diol **2** in 45% yield. The spectral data[33] of the synthetic **2** were in good accordance with those of natural theopederin B (**2**).

In summary, the first total synthesis of theopederin B (**2**) was accomplished through coupling of the left and right halves. We had previously obtained the left half. The right half was synthe-



Scheme 3.



Scheme 4.

sized via SmI_2-promoted intramolecular Reformatsky-type reaction, insertion of the side chain and functionalization, and construction of the 4-amino-1,3-dioxadecaline ring.

Acknowledgment

We thank Professor Shigeki Matsunaga (Tokyo University) for providing the NMR spectrum of natural theopederin B.

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23. *Data for* **9**: mp 195–197 °C; $[\alpha]_D^{23}$ +3.8 (*c* 1.06, $CHCl_3$); IR (KBr) 3363, 2995, 2885, 1699, 1398, 1214, 1110, 1056, 1003 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.46–7.44 (m, 2H), 7.38–7.36 (m, 3H), 5.54 (s, 1H), 4.58 (m, 1H), 4.45 (dd, *J* = 13.1, 1.2 Hz, 1H), 4.26 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.09 (dd, *J* = 13.1, 1.8 Hz, 1H), 3.89 (d, *J* = 3.4 Hz, 1H), 1.46 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.6, 137.2, 129.2, 128.3, 126.1, 101.3, 74.7, 73.4, 69.9, 69.5, 41.8, 27.0, 23.0; HRMS (FAB) calcd for $C_{15}H_{18}O_5Na$ (M+Na$^+$) 301.1046, found 301.1043.
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27. *Data for* **13**: $[\alpha]_D^{23}$ +59.5 (*c* 1.03, $CHCl_3$), IR (neat) 3469, 3067, 3031, 2933, 1641, 1497, 1469, 1455, 1389, 1363, 1206, 1173, 1103, 918 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.27 (m, 5H), 5.88–5.80 (m, 1H), 5.13–5.08 (m, 2H), 4.69 (d, *J* = 11.3 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.12 (ddd, *J* = 9.8, 6.7, 5.2 Hz, 1H), 3.90 (ddd, *J* = 11.9, 9.8, 2.4 Hz, 1H), 3.79–3.74 (m, 2H), 3.57 (s, 3H), 3.27 (dd, *J* = 10.4, 2.1 Hz, 1H), 2.96 (d, *J* = 9.5 Hz, 1H), 2.22–2.18 (m, 1H), 2.13–2.09 (m, 1H), 2.04 (dd, *J* = 9.2, 2.4 Hz, 1H, OH), 0.97 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHZ, $CDCl_3$) δ 138.0, 135.9, 129.5, 128.3, 127.7, 127.6, 117.0, 85.5, 77.7, 76.6, 73.2, 69.9, 62.1, 58.5, 41.1, 33.2, 14.3, 14.2; HRMS (FAB) calcd for $C_{19}H_{29}O_4$ (M+H$^+$) 321.2060, found 321.2065.

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30. *Data for* **20**: $[\alpha]_D^{24}$ +27.5 (*c* 1.15, $CHCl_3$); IR (neat) 3501, 2952, 2833, 1737, 1438, 1370, 1248, 1195, 1164, 1107, 1020, 964, 928, 898, 757, 610 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHZ) δ 5.07–5.01 (m, 1H), 4.73 (d, *J* = 5.8 Hz, 1H), 4.01 (dd, *J* = 5.8, 5.8 Hz, 1H), 3.96 (m, 1H), 3.68 (s, 3H), 3.54 (s, 3H), 3.48 (s, 3H), 3.44 (s, 3H), 3.41 (dd, *J* = 10.8, 2.3 Hz, 1H), 3.14 (d, *J* = 3.9 Hz, 1H), 2.92 (d, *J* = 7.5 Hz, 1H), 2.41–2.28 (m, 2H), 2.04 (s, 3H), 1.91–1.85 (m, 1H), 1.78–1.53 (m, 5H), 1.02 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 173.8, 170.5, 102.5, 86.6, 71.8, 70.2, 68.6, 61.4, 55.4, 52.3, 51.4, 39.4, 33.6, 33.0, 31.7, 24.6, 21.2, 20.4, 16.3; HRMS (FAB) calcd for $C_{20}H_{36}O_9Na$ ($M+Na^+$) 443.2252, found 443.2264.
31. The mixture of α- and β-azides **22** was used for the next hydrogenation, although they are separable.
32. The mixture of α- and β-amines **23** was immediately used for the next coupling, because they are unstable.
33. *Data for the synthetic* **2**: $[\alpha]_D^{22}$ +59.7 (*c* 0.29, $CHCl_3$); IR (neat) 3356, 3072, 2925, 2853, 1732, 1690, 1520, 1455, 1383, 1303, 1263, 1196, 1173, 1108, 1302, 1263, 1196, 1173, 1108, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.47 (d, *J* = 9.2 Hz, 1H), 1.90 (dd, *J* = 9.5, 9.5 Hz, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 4.89 (d, *J* = 7.0 Hz, 1H), 4.86 (br s, 1H), 4.75 (br s, 1H), 4.31 (d, *J* = 2.4 Hz, 1H), 4.23 (dd, *J* = 10.5, 7.0 Hz, 1H), 4.02 (dq, *J* = 6.7, 2.7 Hz, 1H), 3.92 (d, *J* = 2.4 Hz, 1H), 3.86 (dd, *J* = 9.8, 6.7 Hz, 1H), 3.66 (s, 3H), 3.65 (br, 2H), 3.57 (s, 3H), 3.47 (d, *J* = 10.1 Hz, 1H), 3.32 (s, 3H), 2.41–2.38 (m, 2H), 2.33 (t, *J* = 7.6 Hz, 2H), 2.26 (dq, *J* = 7.0, 2.4 Hz, 1H), 1.76–1.30 (m, 6H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 174.2, 171.8, 145.6, 110.6, 99.8, 86.9, 80.3, 79.0, 74.4, 73.8, 72.7, 71.2, 70.1, 69.6, 61.8, 51.5, 48.8, 41.6, 41.3, 36.5, 35.5, 33.8, 33.7, 23.1, 20.8, 17.9, 13.6, 12.1; HRMS (FAB) calcd for $C_{28}H_{47}NO_{11}Na$ ($M+Na^+$) 596.3041, found 596.3055.