Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1553–1557

TETRAHEDRON LETTERS

Synthesis of dihydroxylated prolines and iminocyclitols from five-membered endocyclic enecarbamates. Total synthesis of the potent glycosidase inhibitor (2*R*,3*R*,4*R*,5*R*)-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP)

Ariel Lázaro L. Garcia and Carlos Roque D. Correia*

Instituto de Química, Universidade Estadual de Campinas, CP 6154, 13083-970, Campinas, SP, Brazil

Received 4 December 2002; revised 23 December 2002; accepted 2 January 2003

Abstract—*cis*- and *trans*-3,4-Dihydroxylated prolines and the iminocyclitol 1,4-dideoxy-1,4-imino ribitol were synthesized employing a strategy involving the Heck arylation of five-membered endocyclic enecarbamates with aryldiazonium salts followed by oxidative cleavage of the electron-rich aromatic ring. The total synthesis of the potent α- and β-glucosidase inhibitor (2*R*,3*R*,4*R*,5*R*)-2,5-hydroxymethyl-3,4-dihydroxypyrrolidine (DMDP) was also achieved by the same strategy in ten steps from a chiral five-membered enecarbamate in 12% overall yield.

Polyhydroxylated pyrrolidines and polyhydroxylated pyrrolizidines, commonly referred to as iminocyclitols or azasugars, are monosaccharide mimics acting as transition-state analogues to oligosaccharide processing enzymes, such as glycosidases, mannosidases, galactosidases and glycosyltransferases.[1] As these enzymes are involved in many physiological and pathological processes such as cancer metastasis, viral infection and immunological responses, among others, their selective inhibition is seen as an outstanding opportunity for the development of new drugs and therapeutical agents.[1b] Undoubtedly, the iminocyclitols are among the most active compounds inhibiting carbohydrate processing enzymes, and it has been postulated that their activity is due to the oxacarbenium-ion-like transition state which arises from the protonation of the heterocyclic nitrogen at physiological pH.[2]

For the last few years, we have been working on the Heck arylation of endocyclic enecarbamates and pyrrolines using arenediazonium salts as an effective way of introducing aromatic rings onto a heterocyclic framework.[3] These investigations have been motivated by the large number of bioactive natural and unnatural heterocyclic compounds possessing an aromatic ring α to a heterocyclic nitrogen on a pyrrolidine ring. In particular, electron-rich aromatic systems have been incorporated efficiently by Heck arylations. Moreover, the electronic nature of the aromatic rings makes them function as masked functional groups, thus allowing access to other important functionalities, such as carboxylic acids and/or hydroxymethyl groups. Application of this synthetic methodology was seen as a concise entry for the preparation of cyclic aminoacids and iminocyclitols from 2-arylpyrrolines, according to Figure 1.[4]

In this paper we describe the application of such a strategy to the synthesis of *trans*- and *cis*-3,4-dihydroxyprolines (±)-**1** and (±)-**2**, and iminocyclitol 1,4-dideoxy-1,4-imino ribitol (±)-**3**, as well as a total synthesis of (2*R*,3*R*,4*R*,5*R*)-2,5-dihydroxymethy-3,4-dihydroxypyrrolidine (DMDP), (+)-**4**,[1b] a potent natu-

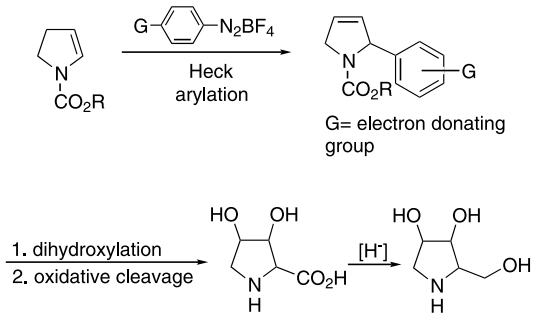


Figure 1.

* Corresponding author. Tel.: +55-19-3788-3086; fax: +55-19-3788-3023; e-mail: roque@iqm.unicamp.br

0040-4039/03/$ - see front matter
PII: S0040-4039(03)00017-0

ral α- and β-glycosidase inhibitor, all from five-membered enecarbamates (Fig. 2).

We started out by preparing 3,4-dihydroxylated prolines and trihydroxy pyrrolidines in racemic form as a testing ground for the synthesis of more complex iminicyclitols. 3,4-Dihydroxyprolines are found as substructures in bioactive natural compounds and an effective methodology for their synthesis has been the subject of much attention in recent years.[5] For example, the 2,3-*trans*-3,4-*trans* dihydroxyproline **1** is a constituent of virotoxin, isolated from *Amantia virosa*,[6] and the 2,3-*trans*-3,4-*cis* dihydroxyproline **2** is found as a constituent of the repeating decapeptide sequence of the adhesive protein Mefp1 produced by the marine mussel *Mytilus edulis*.[7]

Synthesis of the racemic 2,3-*trans*-3,4-*trans* dihydroxyproline **1** was accomplished from the five-membered enecarbamate **5** in six steps (Scheme 1). Heck arylation of enecarbamate **5** with *p*-methoxybenzenediazonium salt in acetonitrile gave the desired 2-arylpyrroline **6** in 83% yield, without any detectable amounts of isomerized Heck adducts. Epoxidation of **6** with *m*-cloroperbenzoic acid (*m*-CPBA) provided only moderate yields (~ 50%) of the *trans*-epoxide **7** as the major diastereomer (dr>96:4) despite several attempts to increase the yields for this transformation. Regioselective epoxide opening was accomplished under acidic conditions to provide the *trans*-diol **8a**, which was converted into the diacetate **8b** prior to oxidative cleavage in 77% yield (over two steps). Oxidative cleavage of **8b** with catalytic $RuCl_3$, following the procedure of Sharpless–Shioiri,[8] gave the corresponding diacetate carboxylic acid (78% yield), which was then hydrolyzed with 7N HCl to furnish the desired 2,3-*trans*-3,4-*trans* dihydroxyproline **1** in 70% yield.

For the synthesis of the 2,3-*trans*-3,4-*cis* dihydroxyproline (±)-**2** a similar strategy was employed. Standard dihydroxylation of arylpyrroline **6** with cat. $K_2OsO_2(OH)_4$ in the presence of *N*-methylmorpholine oxide (NMO) gave the expected 3,4-*cis*-diol in 94% yield with a stereoselectivity of 139:1 as measured by cap. GC. The intermediate diol was then acetylated as before (acetic anhydride, pyridine, DMAP, quantitative yield) to furnish the diacetate **9**. Oxidative cleavage of the *p*-methoxybenzene ring using cat. $RuCl_3/NaIO_4$ provided the corresponding protected aminoacid **10** (82% yield) which, by acidic hydrolysis, furnished the desired 2,3-*trans*-3,4-*cis*-dihydroxyproline (±)-**2** in 71% yield (Scheme 2).

The synthesis of the iminocyclitol (±)-**3** was accomplished in a straightforward manner. The protected amino acid **10** was converted into an intermediate methyl ester by reaction with CH_2N_2 (quantitative yield) and then reduced with $NaBH_4$ in the presence of $CaCl_2$ (57% yield).[9] The resulting primary alcohol **11** underwent acidic hydrolysis with 7N HCl to provide the racemic 1,4-dideoxy-1,4-imino ribitol (±)-**3** in 98% yield (Scheme 3).

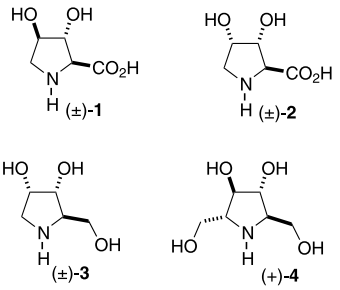
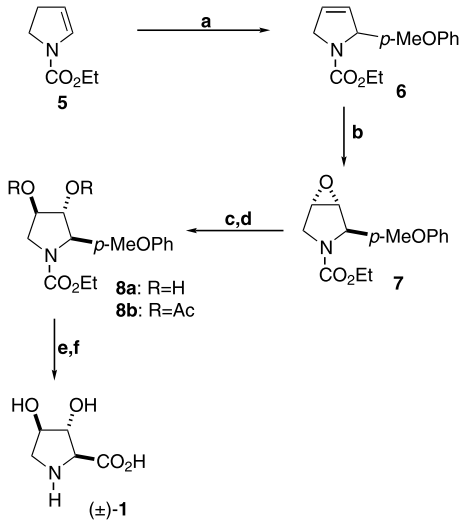
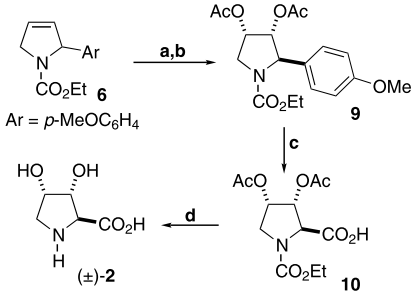


Figure 2.

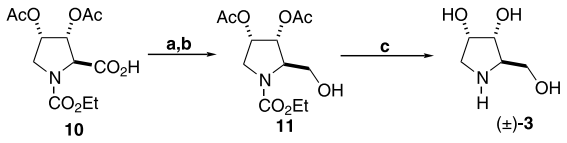


Scheme 1. *Reagents and conditions*: (a) *p*-$MeOC_6H_4N_2BF_4$, $Pd_2(dba)_3$·dba, NaOAc, CH_3CN, 30°C; (b) *m*-CPBA, CH_2Cl_2; (c) dioxane/H_2O/H_2SO_4, reflux, 2.5 h; (d) Ac_2O, Py, DMAP, CH_2Cl_2; (e) $NaIO_4$, cat. $RuCl_3$, EtOAc/CH_3CN/H_2O; (f) 7N HCl, reflux, 18 h, then Dowex 50Wx8-400.



Scheme 2. *Reagents and conditions*: (a) NMO, $K_2OsO_2(OH)_4$, H_2O/acetone/*t*-BuOH; (b) Ac_2O, Py, DMAP, CH_2Cl_2; (c) $NaIO_4$, cat. $RuCl_3$, EtOAc/CH_3CN/H_2O; (d) 7N HCl, reflux, then Dowex 50Wx8-400.

With the above groundwork concluded we turned our attention to the total synthesis of more complex iminocyclitols possessing important biological functions. We were particularly interested in the total synthesis of



Scheme 3. *Reagents and conditions*: (a) CH_2N_2, CH_3OH (100%); (b) $NaBH_4$, CH_3OH/THF, $CaCl_2$, rt, 8 h (57%); (c) 7N HCl, reflux, 18 h, then Dowex 50Wx8-400 (98%).

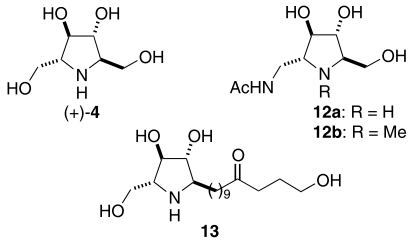
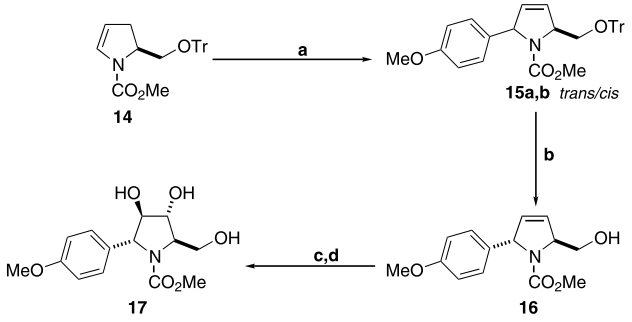


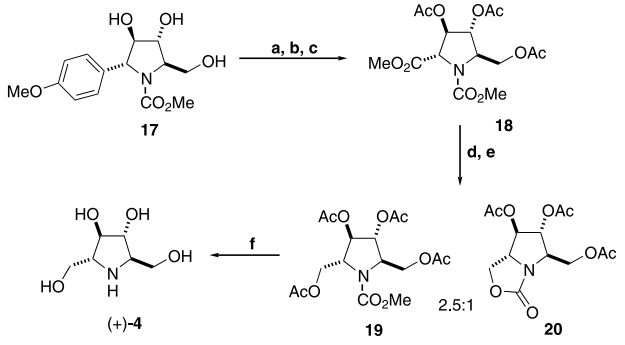
Figure 3.

the important (2*R*,3*R*,4*R*,5*R*)-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP),[10] (+)-**4**, by a flexible route which would potentially allow the synthesis of analogues, such as the (2*R*,3*R*,4*R*,5*R*)-2-(acetamidomethyl)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidine **12a** and broussonetine C, **13** (Fig. 3). All three iminocyclitols exhibit strong glicosidase inhibition activity in the micromolar range. DMDP is a strong inhibitor of α- and β-glycosidase,[1b] the amino derivatives **12a**,**b** are potent inhibitors of β-*N*-acetylglucosaminidase,[11] whereas broussonetine C[12] is a galactosidase and β-mannosidase inhibitor.

The first stage of the synthetic route was closely related to a previously reported work[3b] in which endocyclic enecarbamates are efficiently arylated with aryldiazonium salts. Heck arylation of the chiral enecarbamate **14** with *p*-methoxybenzenediazonium tetrafluoroborate provided the arylpyrrolidines **15a**,**b** in 95% yield as a 87:13 mixture of *trans* and *cis* diastereomers (Scheme 4). Removal of the trityl group with formic acid followed by chromatographic separation provided the desired 2,5-*trans* pyrroline **16** in an isolated yield of 70%. Substrate directed epoxidation of **16** then gave the β-epoxypyrrolidine as the sole product in an 80% yield. Stereoselective epoxide opening under acidic conditions furnished the trihydroxylated pyrrolidine **17** in 63% yield.



Scheme 4. *Reagents and conditions*: (a) $Pd_2(dba)_3$·dba (1 mol%), *p*-$MeOC_6H_4N_2BF_4$, NaOAc, CH_3CN, 20 min (95%); (b) HCO_2H, EtOAc, 40 min (70% of **15a** plus 15% of **15b**); (c) *m*-CPBA, toluene, rt, 24 h (80%); (d) dioxane/H_2O/H_2SO_4 (3:2:0.2), reflux, 2.5 h (63%).



Scheme 5. *Reagents and conditions*: (a) Ac_2O, pyridine, DMAP, CH_2Cl_2, 2 h (100%); (b) $RuCl_3$, $NaIO_4$, EtOAc/CH_3CN/H_2O (1:1:10), rt, 3 h (67%); (c) CH_2N_2, MeOH, 15 min (100%); (d) $LiBH_4$, THF, rt, 8 h (57%); (e) Ac_2O, pyridine, DMAP, CH_2Cl_2, 2 h (100%); (f) 7N HCl, reflux, 18 h, then Dowex 50Wx8-400 (97%).

Oxidative cleavage of the *p*-methoxybenzene substituent of **17** followed the same strategy described previously, that is, protection of the hydroxyl groups in the form of acetate, cleavage using cat. $RuCl_3$/$NaIO_4$ and then esterification with diazomethane to provide the triacetate aminoester **18** in 67% yield over three steps (Scheme 5). Attempts to improve the yields of this oxidative cleavage proved unsuccessful. Changes in the amount of cat. $RuCl_3$/$NaIO_4$ or in the reaction time led to no yield improvement. The ester triacetate **18** was reduced with $LiBH_4$ to give a mixture of two very polar polyhydroxylated pyrrolidines, which were directly converted to the more manageable triacetates **19** and **20** in a 2.5:1 ratio. Although both compounds can be easily separated by column chromatography (for preparation of analytical samples, for instance) they were used as mixture in the hydrolysis step with 7N HCl to give the desired DMDP (+)-**4** in almost quantitative yield.

The total synthesis of the natural (2*R*,3*R*,4*R*,5*R*)-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (+)-**4** involved ten steps from the chiral endocyclic enecarbamate **14** and was accomplished with an overall yield of 12%.

The highlights of the above strategy were the very practical and high yielding Heck arylation of endocyclic enecarbamates and the conversion of the electron-rich aromatic ring to the carbomethoxy and hydroxymethyl functionality, which are present in a number of important natural products. Following this strategy we

accomplished the synthesis of racemic 2,3-*trans*-3,4-*trans* and 2,3-*trans*-3,4-*cis* dihydroxyprolines (±)-**1** and (±)-**2** in 17 and 45% overall yields, respectively. In a similar manner the synthesis of the racemic iminocyclitol 1,4-dideoxy-1,4-imino ribitol (±)-**3** was accomplished in 25% overall yield from enecarbamte **5**. The synthetic strategy was amenable to the total synthesis of DMDP (+)-**4** in only ten steps with an overall yield of 12% from the chiral enecarbamate **14**.[13] With the synthesis of DMDP completed, we are currently adapting this strategy to the synthesis of iminocyclitols **12** and **13**. These results will be disclosed in due course.

Acknowledgements

We thank the Research Support Foundation of the State of São Paulo (FAPESP) for financial support of this work (grants 99/06566-7 and 02/03431-8) and for a doctoral fellowship to A.L.L.G. (00/07065-0). We also thank the National Research Council (CNPq) for a research fellowship to C.R.D.C.

References

1. (a) *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stutz, A. E., Ed.; Wiley-VCH: Weinheim, 1999; (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.
2. (a) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1–8; (b) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340–347; (c) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182–190; (d) For an excellent review about glycosidase mechanisms, see: Rye, C. S.; Withers, S. G. *Curr. Opin. Chem. Biol.* **2000**, *4*, 573–580 and references cited therein.
3. (a) Carpes, M. J. S.; Correia, C. R. D. *Tetrahedron Lett.* **2002**, *43*, 741–744; (b) Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039–3042; (c) Carpes, M. J. S.; Correia, C. R. D. *Synlett* **2000**, 1037–1039; (d) Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 2083–2086.
4. During the course of this work similar approaches to the synthesis of 3,4-dihydroxyprolines and 1,4-dideoxy-1,4-imino-D-ribitol were reported by Riera and by Hassner. Both researchers prepared the key 2-arylpyrroline by ring-closing methatesis. For details, see: (a) Martin, R.; Alcón, M.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2002**, *67*, 6896–6901; (b) Kumareswaran, R.; Hassner, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3409–3415.
5. (a) Ref. 4a; (b) Taylor, C. M.; Barker, W. D.; Weir, C. A.; Park, J. H. *J. Org. Chem.* **2002**, *67*, 4466–4474; (c) Taylor, C. M.; Weir, C. A. *Org. Lett.* **1999**, *1*, 787–789; (d) Fujii, M.; Miura, T.; Kajimoto, T.; Ida, Y. *Synlett* **2000**, 1046–1048; (e) Weir, C. A.; Taylor, C. M. *J. Org. Chem.* **1999**, *64*, 1554–1558; (f) Pohlit, A. M.; Correia, C. R. D. *Heterocycles* **1997**, *45*, 2321–2325.
6. Buku, A.; Faulstich, H.; Wieland, T.; Dabrowski, J. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 2370–2371.
7. (a) Taylor, S. W.; Waite, J. H.; Ross, M. M.; Shabanowitz, J.; Hunt, D. F. *J. Am. Chem. Soc.* **1994**, *116*, 10803–10804; (b) Waite, J. H.; Housley, T. J.; Tanzer, M. L. *Biochemistry* **1985**, *24*, 5010–5014; (c) Waite, J. H.; Tanzer, M. L. *Science* **1981**, *212*, 1038–1040.
8. (a) Carisen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938; (b) Matsura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 265–274.
9. Lewis, N.; McKillop, A.; Taylor, R. J. K.; Watson, R. J. *Synth. Commun.* **1995**, *25*, 561–568.
10. For recent syntheses of DMDP, see: (a) Ref. 1a; (b) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203–7214; (c) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1503–1508; (d) For previous syntheses of DMDP, see the following review: Wrodnigg, T. M. *Monatsh. Chem.* **2002**, *133*, 393–426 and references cited therein.
11. Takebayashi, M.; Hiranuma, S.; Kaine, Y.; Kajimoto, T.; Kanie, O.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5280–5291.
12. (a) Yoda, H.; Shimojo, T.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 1335–1336. For isolation of this compound, see: (b) Shibano, M.; Kitagawa, S.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 505–508; (c) Shibano, M.; Kitagawa, S.; Nakamura, S.; Akazawa, N.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 700–705.
13. All new compounds were fully characterized. Selected data for representative compounds: **17**: Light yellow oil; TLC: R_f=0.24 (EtOAc); $[\alpha]_D^{20}$ −34.0 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (500 MHz, DMSO-d_6, rotamers): δ 7.14 and 7.10 (2d, 2H, J=8.5 Hz), 6.82 (apparent t, 2H, J=8.5 Hz), 5.56 and 5.55 (2s, 1H), 5.03 (m, 2H), 4.56 and 4.54 (2s, 1H), 4.07 and 4.01 (2s, 1H), 3.87–3.74 (m, 2H), 3.71 (s, 3H), 3.73–3.60 (m, 2H), 3.54 (s, 1.2H), 3.31 (s, 1.8H); ^{13}C NMR (125 MHz, DMSO-d_6, rotamers): δ 157.6, 157.5, 154.7, 154.2, 134.1, 133.6, 127.5, 127.0, 113.05, 112.98, 83.2, 82.5, 77.8, 77.0, 70.7, 70.1, 68.6, 68.1, 59.8, 58.8, 54.9, 54.8, 51.8, 51.6; HRMS calcd for $C_{14}H_{19}NO_6$ 297.12124, found 297.12136. **18**: Colorless oil; TLC: R_f=0.58 (EtOAc/Hex, 2:1); $[\alpha]_D^{20}$ −18.2 (*c* 1.65, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6, rotamers): δ 5.56 and 5.54 (2s, 1H), 5.36 and 5.34 (2s, 1H), 4.81 (1s, 0.4H), 4.72 (dd, 0.5H, J=4.6 and 11.0 Hz), 4.65 (apparent t, 0.5H, J=9.5 Hz), 4.64 (s, 0.5H), 4.52 (dd, 0.5H, J=4.6 and 9.5 Hz), 4.46–4.35 (m, 1.4H), 3.39 and 3.38 (2s, 3H), 3.30 and 3.26 (2s, 3H), 1.77 and 1.75 (2s, 3H), 1.60 and 1.56 (2s, 3H), 1.43 and 1.37 (2s, 3H); ^{13}C NMR (125 MHz, C_6D_6, rotamers): δ 170.4, 170.3, 168.89, 168.86, 168.77, 168.6, 168.5, 168.3, 155.2, 155.0, 78.4, 77.4, 77.3, 76.0, 66.1, 65.4, 64.2, 63.2, 61.8, 61.2, 52.7, 52.6, 52.20, 52.17, 20.41, 20.38, 20.13, 20.10, 20.0, 19.9; HRMS calcd for [$C_{15}H_{21}NO_{10}$+1] 376.12437, found 376.12457. **19**: Colorless oil; TLC: R_f=0.33 (EtOAc/Hex, 1:1); $[\alpha]_D^{20}$ −28.4 (*c* 0.36, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6, rotamers): δ 5.44 and 5.41 (2s, 2H), 4.85 (dd, 1H, J=4.4 and 10.2 Hz), 4.54 (t, 1H, J=10.2 Hz), 4.45 (dd, 1H, J=4.4 and 10.2 Hz), 4.37 (dd, 1H, J=4.4 and 10.2 Hz), 4.29 (t, 1H, J=10.2 Hz), 4.18 (dd, 1H, J=4.4 and 10.2 Hz), 3.38 (s, 3H), 1.72 (s, 6H), 1.53 (s, 6H); ^{1}H NMR (300 MHz, C_6D_6, T=70°C): δ 5.38 (s, 2H), 4.60 and 4.42 and 4.24 (3bs, 6H), 3.42 (s, 3H), 1.76 (s, 6H), 1.60 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6, rotamers): δ 170.1, 170.0, 168.9, 168.8, 154.3, 77.5, 76.5, 64.2, 63.2, 61.6, 60.9, 52.6, 20.5,

20.4; HRMS calcd for [$C_{16}H_{23}NO_{10}$+1] 390.14002, found 390.14052. **20**: Colorless oil; TLC: R_f=0.22 (EtOAc/Hex, 1:1); $[\alpha]_D^{20}$ −44.4 (*c* 0.21, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.22 (apparent t, 1H, J=2.2 Hz), 4.89 (dd, 1H, J=3.7 and 5.9 Hz), 4.61 (d, 2H, J=5.9 Hz), 4.36 (dd, 1H, J=5.9 and 11.0 Hz), 4.28–4.14 (m, 2H), 3.97 (apparent q, 1H, J=5.9 Hz), 2.13 and 2.11 and 2.09 (3s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 170.1, 169.7, 159.9, 82.0, 79.8, 67.5, 63.1, 62.7, 62.5, 20.8, 20.7, 20.6; HRMS calcd for [$C_{13}H_{17}NO_8$+1] 316.10324, found 316.10321.