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Addition of trialkylaluminum reagents to glyconolactones. Synthesis of 1-*C*-methyl GlcNAc oxazoline and thiazoline

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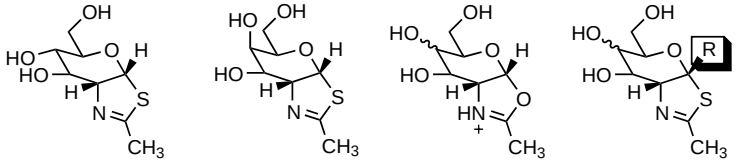
Abstract—Addition of carbon nucleophiles to 2-acetamido-2-deoxygluconolactones fails for many reagents, but trialkylaluminums add alkyl smoothly. The product of methyl addition to 2-acetamido-2-deoxy-D-gluconolactone has been converted to 1-*C*-methyl GlcNAc thiazoline, a potential *N*-acetylhexosaminidase inhibitor, and to an *O*-protected 1-*C*-Me GlcNAc oxazoline, a potential 1-*C*-Me GlcNAc donor. © 2002 Elsevier Science Ltd. All rights reserved.

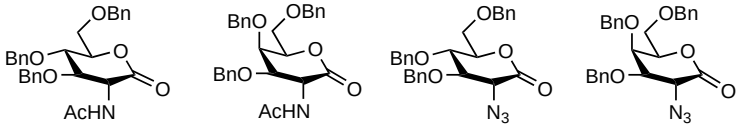
GlcNAc and GalNAc thiazolines **1** and **2** are powerful inhibitors of certain *N*-acetylhexosaminidases because they mimic the presumed oxazolinium intermediate **3**, but are not themselves cleaved by the enzyme.[1,2] We sought to modify **1** and **2** by incorporating substructures, including 1-*C*-alkyl substituents ('R' in box in **4**), that might occupy the aglycon hole and thus increase inhibition by bisubstrate (linkage-bridging) binding.[3] Addition of carbon nucleophiles to 2-acetamido-2-deoxyglyconolactones **5** and **6**, or their 2-azido-2-deoxy equivalents **7** and **8**, represents a possible entry to this class of higher sugars.[4]

Despite numerous reports of nucleophilic carbon addition to sugar lactones,[5,6] and a few examples of the addition of carbon nucleophiles to **5**/**6**,[7] **7**/**8**,[8] and related lactones,[9] we were unable to isolate a clean monoadduct from reactions of **5** or **6** with Wittig reagents, Tebbe reagent, DMT,[10] organolithium reagents, or Grignard reagents. The competing side reactions include NH deprotonation, lactone ring opening, and elimination of the C-3 benzyloxy substituent. The mildly Lewis acidic trialkylaluminum reagents, however, proved to be well suited for this purpose (Scheme 1).

The combination of lactone **5** (3.1 mmol), and trimethylaluminum (6.8 mmol) in 6:1 CH_2Cl_2/toluene solution showed no reaction at –40°C according to TLC analysis, but upon warming to 0°C, the lactone was consumed over a 4 h period. The reaction was quenched with saturated aq. NH_4Cl, and extracted with ethyl acetate, which was washed sequentially with 0.5 N HCl, water, and brine. Chromatography on silica with



1 **2** **3** **4**



5 **6** **7** **8**

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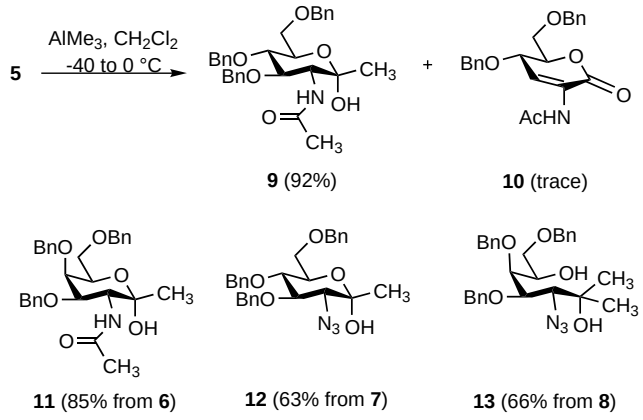


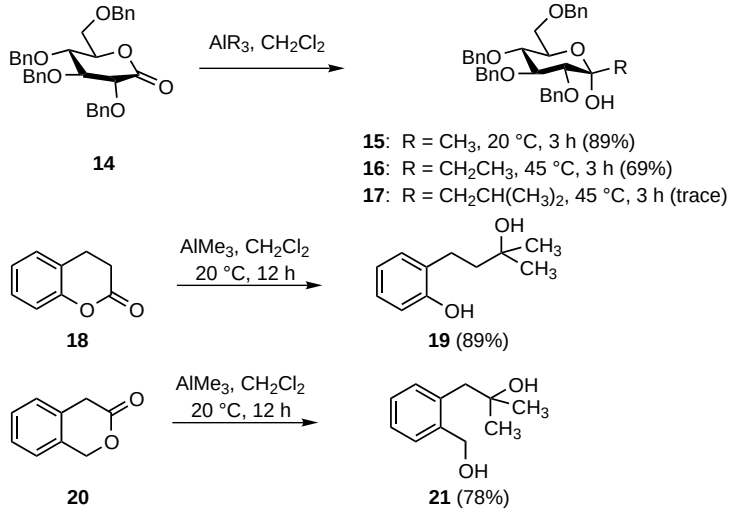
Scheme 1. Reaction of $AlMe_3$ with 2-acetamido/azido-2-deoxy-glyconolactones.

7:7:1 hexanes/ethyl acetate/methanol as the eluant afforded the carbinol **9** as a colorless syrup (92%). The α-anomeric stereochemistry is assigned based on the anomeric effect and literature precedent.[5–9] A trace of the elimination product **10** was also detected by TLC and ^1H NMR.[11] Under the same conditions, the galactonolactone **6** gave the monoadduct **11** (85%). The reactions stop cleanly at the monoaddition stage, as neither TLC nor ^1H NMR provided any evidence for double-addition products derived from **5** or **6**. With only 1 equiv. of $AlMe_3$ at 0°C, no addition to **5** occurred in 4 h, and upon warming to 20°C, **10** formed as the major product.

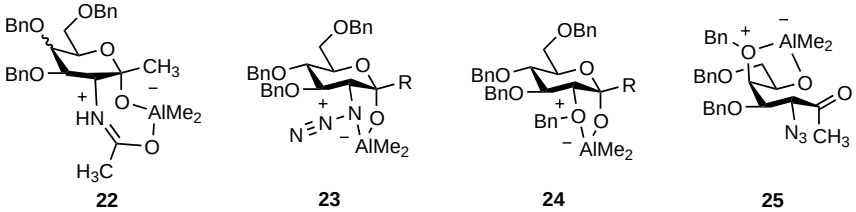
The azidolactones **7** and **8**, however, showed a divergent pattern of reactivity. Addition of $AlMe_3$ to **7** did not occur until the reaction was warmed to 20°C, whereupon slow (12 h) conversion to monoadduct **12** (63% isolated) took place. In the *galacto* series, addition to **7** also took place over 12 h, but the reaction could not be stopped at the monoadduct. Instead, conversion to the bis-adduct **13** occurred (66%), with no evidence for the monoadduct even in the presence of limiting $AlMe_3$.

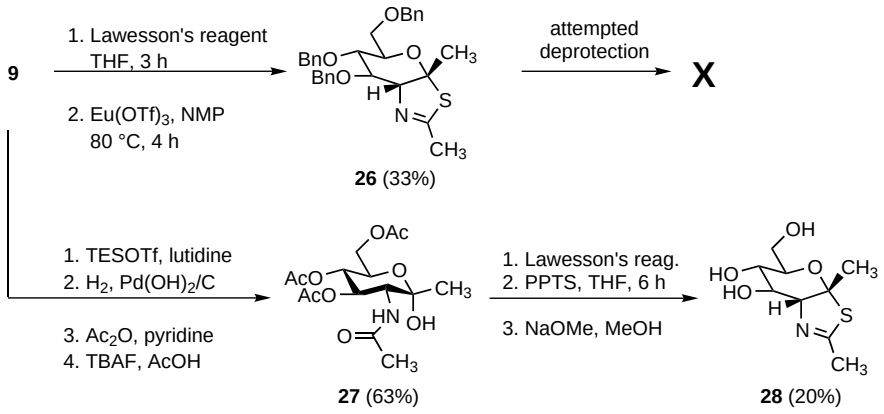
As ordinary esters are inert to these conditions,[12] the reaction of some other lactones with trialkylaluminum reagents was investigated (Scheme 2). Tetra-*O*-benzylgluconolactone[13] **14** gave the known[6] monoadduct **15** with $AlMe_3$, and, under more forcing conditions with $AlEt_3$, the ethyl adduct **16**. $Al(i\text{-}Bu)_3$, however, reacted very slowly, even at 45°C, suggesting a steric limit to this reaction. The simpler lactones dihydrocoumarin **18** and 3-isochromanone **20** gave only the bis-adducts **19** and **21**, respectively.

The reactivity of the carbonyl group of the starting material or its $AlMe_3$ Lewis acid–base complex determines whether addition occurs, and the stability of the initial alkoxyaluminum tetrahedral adduct determines whether a second addition occurs. In the family of 2-substituted gluconolactones **5**, **12**, and **14**, the relative reactivity follows the order: 2-NHAc>2-N_3>2-OBn. Based strictly on inductive effects[14] (σ_I) of the 2-substituent, the expected order of reactivity would be 2-N_3>2-NHAc≈2-OBn. The enhanced reactivity of **5** can be ascribed to prior complexation of $AlMe_3$ with the acetamido group. Likewise, the stability of the initial adduct must be adequate in the cases of **22** (proposed from **5**/**6**), **23** (from **7**), and **24** (from **14**), but not for the initial adduct from **8**, which instead adds a second



Scheme 2. Reaction of AlR_3 with other lactones.





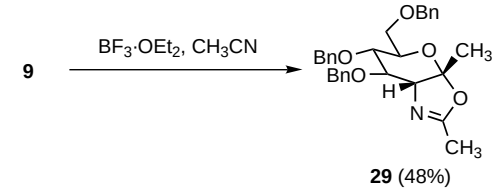
Scheme 3. Synthesis of 1-*C*-methyl GlcNAc thiazoline.

methyl to a ring opened ketone complex that may resemble **25**. Intramolecularly stabilized initial alkoxyaluminum tetrahedral adducts are not possible for **18** and **20**, and this may account for the exclusive double addition observed in these two examples.

Methyl adduct **9** was converted to the 1-*C*-methyl thiazoline target **28** as shown in Scheme 3. Treatment with Lawesson's reagent[1] gave a crude thioamide (76%), which was cyclized to thiazoline **26** (43%) by treatment with the mild Lewis acid $Eu(OTf)_3$ in *N*-methylpyrrolidone solution. Other solvents (benzene, toluene, THF) and protic acids (PPTS) gave similar or poorer yields, and prior conversion of the tertiary anomeric hydroxyl to an acetate or mesylate derivative did not help. Very likely the anomeric leaving group must be in an equatorial position[15] (i.e. β) for cyclization to occur with *S*-participation, and thus a prior inversion at C-1 may be required.

A variety of hydrogenolysis catalysts and conditions were tried for the removal of the *O*-benzyls of **26**, but without success. The sulfur atom evidently poisons the catalysts, and at temperatures much above 23°C the thiazoline ring is destroyed. Trimethylsilyl iodide[16] caused decomposition, and sodium/ammonia reduced the thiazoline competitively. The *O*-benzyl groups were therefore replaced by *O*-acetyl by employing the four step sequence shown in Scheme 3, beginning with *O*-silylation of the anomeric hydroxyl. The resulting tetraacetate **27** reacted smoothly with Lawesson's reagent to provide the crude thioamide, and cyclization was achieved in low yield with pyridinium *p*-toluenesulfonate. Methanolysis of the acetates gave the 1-*C*-methyl GlcNAc thiazoline **28**, which showed the diagnostic five-bond H-2/methyl coupling ($J=1$ Hz) in the ^{1}H NMR spectrum.[1] Although the route to **28** is inefficient, it provides the first entry into this class of 1-*C*-substituted thiazolines (**4**), and may serve as the basis for further structural variations.

Another useful transformation of the methyl adduct **9** is cyclization to the oxazoline **29**, which was achieved by treatment with BF_3 for 2 h at −5°C, and then 10 min at 20°C (Scheme 4). Silica chromatography gave the



Scheme 4. Synthesis of a 1-*C*-methyl GlcNAc oxazoline.

product, which again showed the five-bond ^{1}H NMR coupling that is characteristic of these heterocycles.[17] An attempt at *O*-deprotection of **29** by hydrogenolysis led only to decomposed material, as commented upon by others.[18] GlcNAc oxazolines are useful as glycosyl donors,[19,20] and **29** is the first example of a 1-*C*-substituted representative.

Additional studies will be required to expand the scope of the organoaluminum/glyconolactone reaction, and determine the biological activity of 1-*C*-substituted GlcNAc thiazolines related to **28** and the glycosyl donor properties of 1-*C*-substituted GlcNAc oxazolines related to **29**.[21]

Acknowledgements

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References

1. Knapp, S.; Vocadlo, D.; Gao, Z.; Kirk, B.; Lou, J.; Withers, S. G. *J. Am. Chem. Soc.* **1996**, *118*, 6804–6805.
2. Mark, B. L.; Vocadlo, D. J.; Knapp, S.; Triggs-Raine, B. L.; Withers, S. G.; James, M. N. G. *J. Biol. Chem.* **2001**, *276*, 10330–10337.
3. For some recent examples, see: (a) Häusler, H.; Rupitz, K.; Stütz, A. E.; Withers, S. G. *Monatsh. Chem.* **2002**, *133*, 555–560; (b) Pearson, W. H.; Guo, L. *Tetrahedron Lett.* **2001**, *42*, 8267–8271; (c) Rognigg, T. M.; Withers, S. G.; Stütz, A. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1063–1064; (d) Kondo, K.-I.; Adachi, H.; Nishimura, Y.;

Takeuchi, T. *Nat. Prod. Lett.* **2001**, 371–375; (e) Ramana, C. V.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1599–1610; (f) Panday, N.; Canac, Y.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 58–79; (g) Billault, I.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 1137–1149; (h) Vonhoff, S.; Pins, K.; Pipelier, M.; Braet, C.; Claeyssens, M.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 963–980.

4. Lactone **6** was prepared by hydrogenation of **8** over Raney-Ni in the presence of Ac_2O. Lactones **5**, **7**, and **8** were prepared by Swern oxidation of the corresponding lactols. See: Ayadi, E.; Czernecki, S.; Xie, J. *J. Carbohydr. Chem.* **1996**, *15*, 191–199.
5. For recent examples and leading references, see: Yang, W.-B.; Yang, Y.-Y.; Gu, Y.-F.; Wang, S.-H.; Chang, C.-C.; Lin, C.-H. *J. Org. Chem.* **2002**, *67*, 3773–3782.
6. Li, X.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4297–4309.
7. (a) Molina, A.; Czernecki, S.; Xie, J. *Tetrahedron Lett.* **1998**, *39*, 7507–7510; (b) Xie, J.; Molina, A.; Czernecki, S. *J. Carbohydr. Chem.* **1999**, *18*, 481–498.
8. (a) Dondoni, A.; Marra, A.; Pasti, C. *Tetrahedron: Asymmetry* **2000**, *11*, 305–317; (b) Ayadi, E.; Czernecki, S.; Xie, J. *Chem. Commun.* **1996**, 347–348; (c) Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404–6412.
9. (a) Lane, J. W.; Halcomb, R. L. *Tetrahedron* **2001**, *57*, 6531–6538; (b) Koviach, J. L.; Chappell, M. D.; Halcomb, R. L. *J. Org. Chem.* **2001**, *66*, 2318–2326.
10. Li, X.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Synlett* **2001**, 1885–1888.
11. Heightman, T. D.; Ermert, P.; Klein, D.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 514–532.
12. Chung, E.-A.; Cho, C.-W.; Ahn, K. H. *J. Org. Chem.* **1998**, *63*, 7590–7591.
13. Kuzuhara, H.; Fletcher, H. G., Jr. *J. Org. Chem.* **1967**, *32*, 2531–2534.
14. Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119–251.
15. Colon, M.; Staveski, M. M.; Davis, J. T. *Tetrahedron Lett.* **1991**, *32*, 4447–4450.
16. Gaurat, O.; Xie, J.; Valéry, J.-M. *Tetrahedron Lett.* **2000**, *41*, 1187–1189.
17. Srivastava, V. K. *Carbohydr. Res.* **1982**, *103*, 286–292.
18. Ballardie, F. W.; Capon, B.; Dearie, W. M.; Foster, R. L. *Carbohydr. Res.* **1976**, *49*, 79–92.
19. For a recent example, see: Di Bussolo, V.; Liu, J.; Huffman, L. G., Jr.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 204–207.
20. For oxazoline as enzyme substrate, see: Kobayashi, S.; Kiyosada, T.; Shoda, S. *Tetrahedron Lett.* **1997**, *38*, 2111–2112.
21. Spectra for new compounds. Compound **9**: IR (film, cm^{-1}) 3313, 1655; ^1H NMR (400 MHz, $CDCl_3$, δ, mult., integr., J in Hz) 7.18–7.37 (m, 15 H), 5.66 (d, 9.9), 4.84 (d, 11.4), 4.82 (d, 10.8), 4.67 (d, 11.5), 4.60 (d, 12.3), 4.55 (d, 9.9), 4.54 (d, 12.4), 4.07 (t, 10.1), 3.98–4.01 (m, 1 H), 3.77 (t, 10.2), 3.63–3.69 (m, 4 H), 1.87 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.3, 138.5, 138.1, 138.0, 128.3, 128.3, 128.3, 128.0, 127.9, 127.7, 127.7, 127.6, 127.5, 97.6, 80.9, 78.8, 74.8, 74.7, 73.3, 71.5, 69.1, 56.3, 26.4, 23.3; FAB-MS m/z 512 MLi^+. Compound **11**: IR 3300, 1651; ^1H NMR (200 MHz) 7.28–7.33 (m, 15 H), 5.47 (d, 9.8), 4.94 (d, 11.6), 4.74–4.55 (m, 3 H), 4.38–4.49 (m, 3 H), 4.07 (t, 6.5), 3.99 (br s), 3.72 (dd, 10.8, 2.6), 3.56 (d, 6.4, 2 H), 3.18 (br s), 1.95 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR (75 MHz) 170.8, 138.8, 138.4, 138.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 98.5, 77.9, 74.6, 73.8, 72.9, 71.8, 70.5, 69.6, 53.9, 27.2, 23.9; FAB-MS 506 MH^+. Compound **12**: IR 2104; ^1H NMR (300 MHz) 7.16–7.40 (m, 15 H), 4.88 (s, 2 H), 4.80 (d, 10.8), 4.60 (d, 12.0), 4.54 (d, 11.0), 4.52 (d, 12.0), 3.96–4.01 (m), 3.95 (dd, 9.9, 9.0), 3.61–3.73 (m, 3 H), 3.22 (d, 9.9), 1.23 (s, 3 H); ^{13}C NMR (50 MHz) 138.4, 138.3, 138.2, 128.3, 127.8, 127.6, 97.4, 81.2, 79.0, 76.0, 75.4, 73.9, 72.2, 69.2, 68.6, 27.6; ES-MS 490 MH^+. Compound **13**: IR 3438, 2106; ^1H NMR (300 MHz) 7.22–7.36 (m, 15 H), 4.81 (d, 11.4), 4.73 (d, 11.4), 4.72 (d, 11.3), 4.59 (d, 11.4), 4.55 (d, 11.7), 4.49 (d, 11.7), 4.13 (dd, 6.3, 2.4), 3.98–4.07 (m, 1 H), 3.91 (dd, 6.3, 1.8), 3.60 (dd, 9.6, 6.3), 3.50 (dd, 9.6, 6.3), 3.27 (d, 2.4), 2.61 (d, 6.9), 2.45 (s), 1.29 (s, 6 H); ^{13}C NMR (75 MHz) 137.9, 137.8, 137.7, 128.7, 128.7, 128.7, 128.4, 128.3, 128.2, 128.1, 128.1, 127.8, 78.9, 78.8, 75.0, 74.4, 73.8, 73.7, 71.5, 69.7, 68.7, 28.8, 27.5; ES-MS 506 MH^+. Compound **15**: IR 3431; ^1H NMR (400 MHz) 7.27–7.36 (m, 18 H), 7.17–7.19 (m, 2 H), 4.83–4.96 (m, 4 H), 4.72 (d, 11.1), 4.64 (d, 12.3), 4.58 (d, 10.9), 4.55 (d, 12.3), 4.05 (obscd m), 3.98 (t, 9.3), 3.74–3.78 (m), 3.68–3.75 (m, 2 H), 3.39 (d, 9.3), 2.58 (br s), 1.43 (s, 3 H); ^{13}C NMR (100 MHz) 138.6, 138.2, 138.2, 137.8, 128.3, 128.3, 128.2, 128.2, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 97.3, 83.6, 83.1, 78.4, 75.6, 75.5, 74.8, 73.3, 71.5, 68.7, 26.5; FAB-MS 561 MLi^+. Compound **16**: IR 3449; ^1H NMR (400 MHz) 7.17–7.43 (m, 20 H), 4.52–4.82 (m, 3 H), 4.50–4.72 (m, 5 H), 3.91–4.12 (m, 2 H), 3.78 (dd, 11.1, 3.9), 3.72–3.84 (m, 2 H), 3.45 (d, 9.0), 2.52 (br s), 1.73 (dq, 3.3, 7.2, 2 H), 0.91 (t, 7.2, 3 H); ^{13}C NMR (75 MHz) 138.8, 138.5, 138.1, 137.6, 128.6, 128.6, 128.6, 128.5, 127.3, 127.0, 127.9, 127.8, 127.8, 127.7, 98.7, 84.1, 81.5, 78.7, 75.9, 75.7, 75.2, 73.6, 71.9, 69.1, 31.8, 7.28; FAB-MS 575 MLi^+. Compound **21**: IR 3270, 2973, 1496, 1451, 1141, 1011, 784; ^1H NMR (300 MHz) 7.13–7.32 (m, 4 H), 4.84 (br s, 1 H), 4.53 (s, 2 H), 3.58 (br s, 1 H), 2.85 (s, 2 H), 1.27 (s, 6 H); ^{13}C NMR (75 MHz) 140.2, 136.7, 132.4, 130.7, 127.8, 127.0, 70.8, 63.3, 45.6, 30.4; CI-MS 181 MH^+. Compound **26**: IR 1650; ^1H NMR (300 MHz) 7.16–7.39 (m, 15 H), 4.74 (d, 11.7), 4.50–4.65 (m, 4 H), 4.33 (d, 11.7), 4.26 (app quint, 2.1), 4.06 (dd, $J=3.0$, 4.4), 3.59–3.63 (m, 4 H), 2.21 (d, $J=1.8$, 3 H), 1.93 (s, 3 H); ^{13}C NMR (75 MHz) 167.5, 138.4, 138.2, 138.1, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 103.8, 81.6, 79.6, 76.1, 73.5, 73.4, 72.7, 72.5, 70.0, 30.5, 21.9; FAB-MS 510 MLi^+. Compound **27**: IR 3346, 1746, 1657; ^1H NMR (200 MHz) 5.84 (d, 9.9), 5.25 (t, 10.0), 5.10 (t, 9.4), 4.01–4.27 (m, 4 H), 3.53 (br s), 2.08, 2.01, 2.00, 1.97, 1.44 (5 s, 3 H each); ^{13}C NMR (50 MHz) 171.7, 171.4, 170.8, 169.9, 98.2, 72.6, 68.9, 68.8, 62.8, 55.8, 26.5, 23.6, 21.3, 21.2, 21.1; ES-MS 362 MH^+. Compound **28**: ^1H NMR (500 MHz, CD_3OD) 3.80–3.84 (m, 2 H), 3.68 (dd, 12, 6.0), 3.53–3.58 (m, 2 H), 3.38 (dd, 10, 7.0), 2.2 (d, 1.0, 3 H), 1.76 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) 172.3, 105.1, 83.1, 77.8, 77.2, 70.4, 62.9, 31.1, 22.0; ES-MS 234 MH^+. Compound **29**: IR 1669; ^1H NMR (400 MHz, $CDCl_3$) 7.10–7.31 (m, 15 H), 4.60 (d, 12.4), 4.50 (d, 12.4), 4.49 (obscd AB q, 12, 2 H), 4.45 (d, 11.6), 4.20 (d, 12.0), 3.92 (br s, 2 H), 3.43–3.55 (m, 4 H), 1.97 (d, 1.2, 3 H), 1.65 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) *C*=N not obsd, 138.4, 138.1, 137.9, 128.6, 128.5, 128.3, 128.1, 128.0, 128.0, 127.9, 127.0, 108.7, 77.1, 75.1, 73.5, 72.0, 71.7, 71.5, 70.1, 69.3, 26.8, 14.8; ES-MS 488 MH^+.