Pergamon

Tetrahedron Letters 43 (2002) 2505–2509

TETRAHEDRON LETTERS

$Pb(OAc)_4$ mediated hetero-domino transformations: can any unsaturated 1,2-diol be regarded as a substrate?

José Ignacio Candela Lena, Ertan Altinel, Nicolas Birlirakis and Siméon Arseniyadis*

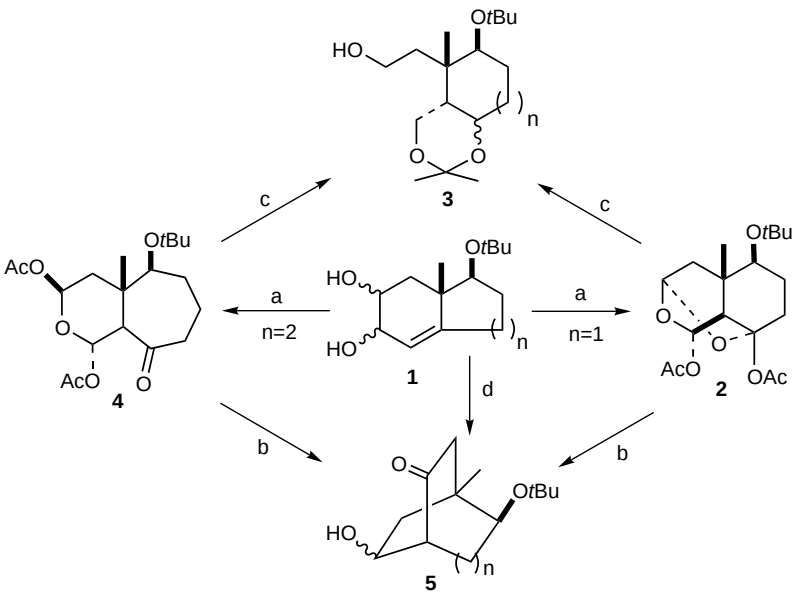
Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette, France

Received 3 February 2002; accepted 16 February 2002

Abstract—We report the oxidative cleavage of unsaturated diols **6** and **7** derived from monocyclic precursors, used as substrates to determine the limits of the olefin as a source of diversity.

One-pot multi-stage transformations are among the most useful synthetic methods available for generating diversity in a single synthetic operation.[1] The unsaturated bicyclic diol system **1** has proven to be a versatile template for the domino transformations during lead tetraacetate mediated oxidative cleavage in the synthesis of taxoid C-ring precursors **2**, **3** ($n=1$)[2] and highly elaborated seven-membered ring containing systems **4**, **5** ($n=2$, Scheme 1).[3]

The reaction protocol successfully accommodated both hydrindene ($n=1$) and octalin diol ($n=2$) bicyclic ring systems **1**, and proved compatible with a large array of functional groups and solvents.[4] The process permits a high number of consecutive bond-breaking/making operations in one synthetic vessel, where one can recognize two important subsets of ''olefin click reactions'':[5] oxidations by electrophilic reagents and cycloaddition reactions. In the absence of the olefin, only the expected



Scheme 1. (a) 2.5 equiv. $Pb(OAc)_4$, MeCN, rt; (b) K_2CO_3-MeOH-H_2O, rt; (c) $LiAlH_4$-Et_2O, 0°C then, acetone, *p*TosOH, (d) 1.2 equiv. $PhI(OAc)_2$, PhMe, rt; then (ca. 24 h) 1 equiv. $Pb(OAc)_4$, then (ca. 15 h) K_2CO_3-MeOH-H_2O, rt.

Keywords: domino reactions; ring-expansion; olefin click reactions; lead tetraacetate; Thorpe–Ingold effect.

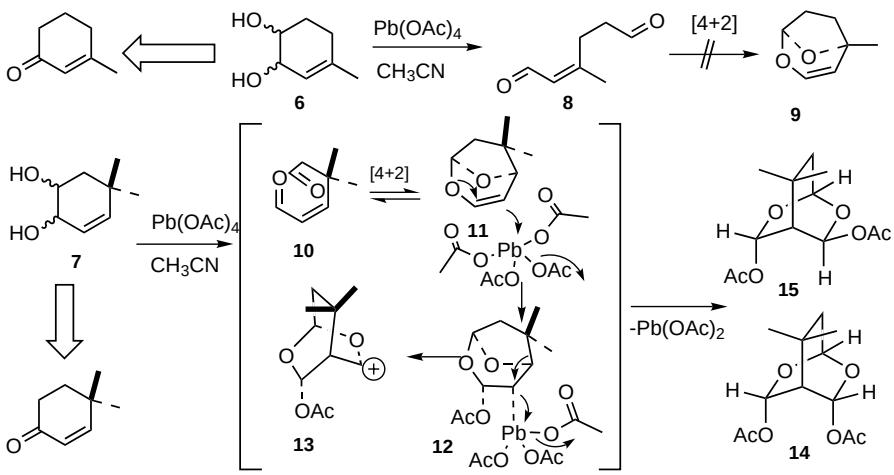
* Corresponding author. Tel.: +33-1-69-82-30-29; fax: +33-1-69-07-72-47; e-mail: simeon.arseniyadis@icsn.cnrs-gif.fr

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00364-7

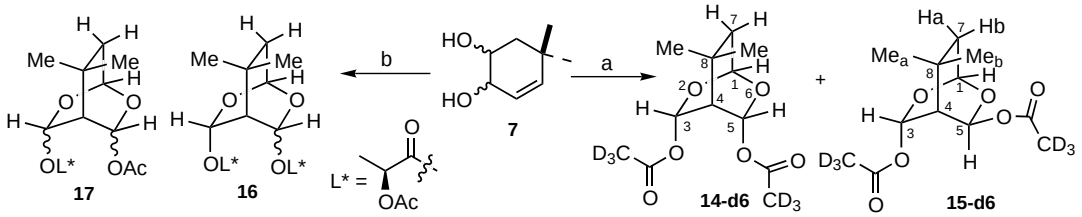
glycol fission was obtained in all cases investigated.[6] Another version of this process, using only one equivalent of lead tetraacetate, is the three-reagent consecutive hetero-domino reaction initiated by iodobenzene diacetate (oxidative/pericyclic transformation),[7] continued by lead tetraacetate (ring expansion) and completed by a mild base consisting of solid K_2CO_3, in MeOH–H_2O (ring system interchange) all in one-pot (route d, Scheme 1).[8] This route represents a remarkable example of maximization of molecular complexity while minimizing waste, where such a high number of transformations are performed without separations. With the aim of extending the synthetic scope of these domino transformations, our attention turned to alternative unsaturated diols that would delineate the scope of the process and, to this end, attention was focused on efforts to build up simpler templates. One could think that any unsaturated diol could be a substrate and thus, using a long connecting chain between the alcohol containing carbons, macrocyclic molecules could have been synthesized following the 4+2 step. In the present paper, we test whether monocyclic unsaturated 1,2-diols will undergo similar reactions. The synthesis of the target substrates **6**[9] and **7** began with the corresponding, commercially available, enones and used the acetoxylation ($Pb(OAc)_4$, PhH, reflux)-reduction ($LiAlH_4$, Et_2O, 0°C) protocol.[10] Upon treatment with $Pb(OAc)_4$, monocyclic unsaturated diol **6** failed to yield any cyclic ene-acetal (such as **9**, Scheme 2) under either set of conditions (varying the solvent and stoichiometry, prolonged heating, adding a Lewis acid such as Ti(*i*PrO)$_4$). Instead, **6** furnished only the dialdehyde **8**, which remained essentially unchanged even after 60 h at 75°C in acetic acid or acetonitrile. This failure is most probably due to the conformational freedom of the internally linked bis-hetero diene/dienophile motif of the resulting dialdehyde **8**; therefore the crucial cyclization to the half-cascade intermediate does not occur.

Diol **7** was designed to overcome this drawback and evaluate the contribution of the Thorpe–Ingold effect.[11] The behavior of **7** is in sharp contrast with that of **6**. Indeed, inserting a *gem*-dimethyl group into the ring system promoted cyclization and thus led to ring expanded full-cascade products, **14** and **15**, arising from the un-isolable half cascade intermediate **11**. Formation of the cyclic ene-acetal **11** was inferred from the NMR spectrum of the crude reaction mixture when only one equiv. of $Pb(OAc)_4$ was used. Upon subjection to our standard cascade conditions, 2.5 equiv. of $Pb(OAc)_4$ in acetonitrile or acetic acid, at room temperature, the *gem*-dimethyl derivative **7** (used as *cis–trans* mixture, but also as pure *cis* or *trans* diols) furnished the dioxa-bicyclo[2.2.2]octane derivatives **14** and **15** in a 9:1 ratio in 62% combined yield after purification. The reaction progress was monitored by TLC and the full cascade products were isolated after 5 h reaction time. The initially formed cycloadduct, cyclic ene-acetal **11**, in equilibrium with the ring opened dialdehyde **10**, readily underwent ring opening to give the ring enlarged compounds **14** and **15**. The diastereomers were separated by flash chromatography, using heptane/ethyl acetate, 3:1 as eluent to afford a 6% yield of **15**, the less polar minor isomer (contaminated with small amounts of **14**), and 56% yield of **14**, the more polar, major isomer.

With regard to the reaction mechanism, the oxidative cleavage/bis-hetero IMDA route is thought to generate the postulated carbocation intermediate **13**. The latter reacts with the acyl group to furnish the corresponding dioxa-bicyclo[2.2.2]octane derivatives **14** and **15**. The key transformation is triggered by an electrophilic attack of the metal on the electron rich double bond of **11**, which sets up the ring expansion process via the transient organolead intermediate **12**. Such reactions of metal on double bonds are well known in literature;[12] the olefin is attacked by the metal, thus creating a carbon–lead bond and bringing the acetate functionalities within reach of the putative carbocationic centers. The structures of the compounds thus obtained were deduced by NMR techniques and by analogy to our earlier results. Assignment of configuration to these two diastereomers was possible by a study of spatial proximity effects using 1D-NOEDIFF.[13] The C-3 (C-5) configuration of **14** followed from NOE experiments where irradiation of methyl (δ 1.30) led to enhance-



Scheme 2.



Scheme 3. (a) $Pb(OAc)_4$, CD_3COOD, rt; (b) $Pb(OAc)_4$, (*S*)-2-acetoxypropionic acid, rt.

ments of the H-3 (H-5) (δ 6.43), H-4 (δ 2.12) and H-7 (δ 1.78) signals. Hence H-3 (H-5) protons must lie on the same face of the molecule confirming the location and the configuration of the 3α-acetoxy group. The minor isomer was assigned as **15** on the basis of diagnostic NOEs for the protons attached to C-3 and C-5 observed upon irradiation of the *gem*-methyl-a and *gem*-methyl-b group signal, respectively. Thus, transannular enhancements were observed between H-3 (δ 6.49) and methyl-a for which the chemical shift was unequivocally established at δ 1.23 on the minor dioxabicyclo[2.2.2]octane derivative **15**. Failure to observe an enhancement at the C-5 H (δ 6.53) on irradiation of the C-8 methyl-b (δ 1.40) group provides evidence that they are on opposite faces of the molecule, an observation in agreement with NMR data, where in the ^1H and ^{13}C NMR spectra, resonances for all protons and carbons were observed due to the lack of symmetry. In the case of **14**, the eight-line ^{13}C NMR spectrum revealed its symmetrical structure.

Consideration of the pathway shown in Scheme 2 suggests that **14** and **15** are derived from the carbocation **13**; this has been validated by carrying out the cascade rearrangements in CD_3CO_2D and (*S*)-*O*-acetyllactic acid ((*S*)-2-acetoxypropionic acid). Domino reactions of **7** conducted at room temperature in CD_3CO_2D proceeded cleanly. The deuterium labeled dioxa-bicyclo[2.2.2]octane derivatives **14-d6** and **15-d6**, were obtained in 66% isolated yield via in situ metathesis (Scheme 3).[14] The ESI mass spectrum of **14-d6** exhibited a molecular ion at *m*/*z* 287 (*M*+Na) and *m*/*z* 303 (*M*+K) consistent with the molecular formula $C_{12}H_{12}D_6O_6$.

A control experiment, in which **14** was stirred in CD_3CO_2D, gave a very low level of exchange; ca. 5% of **14-d6** was detected even after 3 days. Upon treatment with 2 equiv. of $Pb(OAc)_4$ in (*S*)-2-acetoxypropionic acid and proceeding as above, diol **7** gave, following chromatographic purification, **16** (46%; ca. 9:1 ratio) together with **17** (15%), both as an unseparable diastereomeric mixture, characterized as such. The presence of ca. 15% of mixed cascade intermediates **17** can be explained by the competitive pathways involving participation of the reagent's acetate group versus the solvent's one. The observed incorporation of deuterium into the end products **14-d6**, **15-d6** and of the (*S*)-*O*-acetyl lactyl moiety into the end products **16**, **17** rationalizes the mechanism depicted in Scheme 2, where carbocation intermediate **13** originate from the cyclic ene-acetal **11**.

To summarize, in the case of **6**, lacking the rigidity, only the dialdehyde **8** derived from a simple glycol fission was observed. In the case of **7**, containing the *gem*-dimethyl group in the "connecting chain", restriction of conformational freedom enhanced reactivity, since the *gem*-dimethylated analogue underwent cascade transformations. But the Thorpe–Ingold effect, the effect of alkyl substitution to facilitate ring closure reactions, is known to operate only in small rings, and this is a limiting factor. In conclusion, the limits of the $Pb(OAc)_4$-mediated domino transformations are illustrated with two selected examples, revealing an important limitation to the method: any unsaturated olefin cannot be regarded as a substrate.

Structures of products were assigned by comprehensive spectral data (NMR spectra were measured at 300 and 600 MHz ^1H; 75 and 150 MHz ^{13}C, in $CDCl_3$); no special efforts were taken to optimize these reactions.[15]

Acknowledgements

The authors thank the European Commission for a Research Training Grant to Dr. J. I. Candela Lena.

References

1. (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
2. (a) Martín Hernando, J. I.; Quílez del Moral, J.; Rico Ferreira, M.; Candela Lena, J. I.; Arseniyadis, S. *Tetrahedron: Asymmetry* **1999**, *10*, 783–797; (b) Arseniyadis, S.; Brondi Alves, R.; Pereira de Freitas, R.; Muñoz-Dorado, M.; Yashunsky, D. V.; Potier, P.; Toupet, L. *Heterocycles* **1997**, *46*, 727–764; (c) Arseniyadis, S.; Yashunsky, D. V.; Pereira de Freitas, R.; Muñoz-Dorado, M.; Potier, P.; Toupet, L. *Tetrahedron* **1996**, *52*, 12443–12458.
3. (a) Rico Ferreira, M.; Martín Hernando, J. I.; Candela Lena, J. I.; Quílez del Moral, J.; Arseniyadis, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1527–1537; (b) Arseniyadis, S.; Brondi Alves, R.; Quilez del Moral, J.; Yashunsky, D. V.; Potier, P. *Tetrahedron* **1998**, *54*, 5949–5958.
4. (a) Candela Lena, J. I.; Martín Hernando, J. I.; Rico Ferreira, M.; Altinel, E.; Arseniyadis, S. *Synlett* **2001**, 597–600; (b) Martín Hernando, J. I.; Rico Ferreira, M.; Candela Lena, J. I.; Toupet, L.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron: Asymmetry* **1999**, *10*, 3977–3989.

5. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
6. (a) Criegee, R.; Beucker, H. *Ann. Chem.* **1939**, *541*, 218; (b) Candela Lena, J. I.; Rico Ferreira, M.; Martín Hernando, J. I.; Altinel, E.; Arseniyadis, S. *Tetrahedron Lett.* **2001**, *42*, 3179–3182.
7. Candela Lena, J. I.; Altinel, E.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Lett.* **2002**, *43*, 1409–1412.
8. Typical procedure for route "d": To a solution of 5 mmol of the selected unsaturated diol **1** in 50 mL of anhydrous toluene under inert atmosphere, 6 mmol of $PhI(OAc)_2$, 5 mmol of $Pb(OAc)_4$ and 27.5 mmol of K_2CO_3 in 60 mL of $MeOH/H_2O$, 8:1 are added sequentially at room temperature. In both series ($n=1$ and 2), the reaction sequence can be monitored by TLC (heptane/EtOAc, 1:1) with all intermediates and the final products possessing distinct R_f values. A few minutes after addition of $PhI(OAc)_2$, two new higher R_f spots appear on the TLC: a UV active spot (dialdehyde) together with a second, higher R_f, non-UV active one (cyclic ene-acetal). Stirring is maintained under argon for 24 h, at which point $Pb(OAc)_4$ is added; the first two spots disappear and a third non-UV active lower R_f spot, corresponding to **2** ($n=1$) or **4** ($n=2$) appears. Finally, after an extra 15 h stirring, addition of the base completes the transformation. Compounds **5** thus obtained, have been fully characterized in our previous publications (Refs. 2 and 3).
9. Bolton, I. J.; Harrison, R. G.; Lythgoe, B.; Manwaring, R. S. *J. Chem. Soc. (C)* **1971**, 2944–2949.
10. (a) Arseniyadis, S.; Rodriguez, R.; Muñoz Dorado, M.; Brondi Alves, R.; Ouazzani, J.; Ourisson, G. *Tetrahedron* **1994**, *50*, 8399–8426; (b) Arseniyadis, S.; Rodriguez, R.; Brondi, R.; Spanevello, R.; Ouazzani, J.; Ourisson, G. *Microbial Reagents in Organic Synthesis*; Servi, S., Ed; NATO ASI Series C, Kluwer Academic: Dordrecht, 1992; Vol. 381, pp. 313–321.
11. (a) Thorpe, J. F.; Ingold, C. K. *J. Chem. Soc.* **1915**, *107*, 1080; (b) Thorpe, J. F.; Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305.
12. There is substantial precedent for the electrophilic attack of an olefin by metals which react as typical electrophiles; for Tl^{3+}: McKillop, A. *Pure Appl. Chem.* **1975**, *43*, 463–479; for Hg^{2+}: Larock, R. C. *Tetrahedron* **1982**, *38*, 1713–1754; Arseniyadis, S.; Goré, J. *Tetrahedron Lett.* **1983**, *24*, 3997–4000; for Ag^{+}: Arseniyadis, S.; Sartoretti, J. *Tetrahedron Lett.* **1985**, *26*, 729–732; for Pb^{4+}: Levisalles, J.; Molimard, J. *Bull. Soc. Chim. Fr.* **1971**, 2037–2047; Rubottom, G. M. *Oxidation in Organic Chemistry*; Trahanovsky, Part D, Chapter I; Academic Press, 1982.
13. Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703–5711.
14. (a) Bachman, G. B.; Wittman, J. W. *J. Org. Chem.* **1963**, *28*, 65–68; (b) Candela Lena, J. I.; Sesenoglu, Ö.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Lett.* **2001**, *42*, 21–24.
15. Given the fact that $Pb(OAc)_4$ mediated domino transformations are insensitive to diol stereochemistry, the starting diols **6** and **7** were used as diastereomeric mixtures. However, we separated the racemic *cis* and *trans* diols for characterization purposes. Faster eluting *cis*-diol-**6**: IR (film): 3391, 2913, 1667, 1432, 1377, 1262, 1218, 1155, 1119, 1071, 1049, 995, 961, 902, 848 cm^{-1}. ^1H NMR: 1.69 (3H, s), 1.73–2.19 (4H, m), 3.26–3.58 (2H, m), 3.67–3.82 (1H, m), 4.06 (1H, bs), 5.44 (1H, bs). ^{13}C NMR: 23.2, 25.7, 28.5, 66.7, 68.7, 121.6, 139.3. Slower eluting *trans*-diol-**6**: mp: 58–60°C (heptane/ether). IR (film): 3435, 2914, 1673, 1651, 1434, 1377, 1264, 1227, 1155, 1062, 1029, 1007, 970, 937, 905, 875, 807 cm^{-1}. ^1H NMR: 1.67 (3H, s), 1.63–2.20 (4H, m), 3.51–3.61 (1H, m), 3.96–4.31 (2H, m), 4.05 (1H, bs), 5.27 (1H, bs). ^{13}C NMR: 22.7, 28.7, 29.6, 73.5 (2C), 123.1, 136.9. EI MS: 128 ($[M]^+$, 10), 84 (100), 83 (55). Anal. calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44; found: C, 65.54; H, 9.38. **7** (*trans*): mp: 56–58°C (heptane/ether). IR (film): 3418, 2956, 2920, 2864, 1651, 1645, 1633, 1469, 1455, 1361, 1257, 1058, 946, 876 cm^{-1}. ^1H NMR: 1.03 (3H, s), 1.05 (3H, s), 1.49 (1H, t, $J=12.7$), 1.74 (1H, dd, $J=3.2$, 12.7), 3.44–3.87 (2H, m), 3.72 (1H, ddd, $J=3.2$, 7.8, 12.7), 4.04 (1H, d, $J=7.8$), 5.38 (1H, d, $J=10.6$), 5.42 (1H, d, $J=10.6$). ^{13}C NMR: 28.8, 31.0, 34.9, 43.2, 71.7, 74.3, 125.5, 139.0. EI MS: 142 ($[M]^+$, 0.03), 124 (1.5), 109 (1), 98 (100), 86 (20), 83 (10), 55 (10), 41 (10). Anal. calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92; found: C, 67.24; H,10.12. A dry flask was charged with starting diols **7** (123 mg, 0.87 mmol) and $Pb(OAc)_4$ (960 mg, 2.16 mmol, 2.5 equiv.), vacuumed and flushed with argon several times. Dry acetic acid (3 mL) was then added and the reaction mixture was stirred at room temperature for 5 h, at which point TLC indicated complete consumption of starting diols. Dilution with ether followed by washing with saturated aqueous $NaHCO_3$, till neutral pH, and brine, drying over $MgSO_4$, and concentration under reduced pressure afforded 139 mg (62%) of a mixture of **14** and **15**. A careful silica gel, flash column chromatography, eluent heptane/EtOAc, 3:1, allowed separation and hence identification of pure **14**: IR (film): 2968, 1735, 1369, 1223, 1178, 1127, 1050, 962, 872 cm^{-1}. ^1H NMR: 1.30 (6H, s), 1.77–1.79 (2H, m), 2.12 (1H, dd, $J=0.9$, 3.2), 2.14 (6H, s), 4.98 (1H, t, $J=2.1$), 6.43 (2H, d, $J=1.7$). ^{13}C NMR: 21.2 (2C), 28.4 (2C), 29.0, 41.7, 41.8, 91.9 (2C), 92.9, 169.8 (2C). ESI MS: 297 ($[M\mathrm{K}]^+$, 5), 281 ($[M\mathrm{Na}]^+$, 100), 539 ($[2\times M+\mathrm{Na}]^+$, 18). **15** was contaminated with some **14** thus, it was better characterized in its deuterium labeled form, as pure **15-d6**.
Proceeding as above, **7** (152 mg, 1.07 mmol), and $Pb(OAc)_4$ (1185 mg, 2.67 mmol, 2.5 equiv.) were stirred at room temperature in a large excess of deuterated acetic acid (10 mL) for 22.5 h. The large excess of labeled acetic acid is to ensure metathesis of the acetate by the labeled carboxylate, while the extra stirring time is to remove as much as possible the left-over non-labeled acetoxy group, by exchange (and hence to measure the extent of exchange). Work up and flash chromatography using heptane/EtOAc 3:1 as eluent afforded 169 mg (60%) of **14-d6** and 18 mg (6%) of **15-d6**. The unlabeled **14** is present as could be seen from proton, contribution from the unlabeled counterpart at 2.15 (MeCO), from carbon, at 21.2 (MeCO) and Electron Spray Ionization Mass spectra, $C_{12}H_{18}O_6$ at m/z 281 ($[M\mathrm{Na}]^+$, 12), 297 ($[M\mathrm{K}]^+$, 5).
14-d6: IR (film): 2966, 2875, 1725, 1638, 1447, 1368, 1278, 1229, 1178, 1127, 1047, 999, 944 cm^{-1}. ^1H NMR: 1.30 (6H, s, Me-gem), 1.78 (2H, d, $J=2.0$, H-7), 2.12 (1H, t, $J=1.5$, H-4), 5.27 (1H, t, $J=2.0$, H-1), 6.43 (2H, d, $J=1.5$, H-3, H-5). ^{13}C NMR: 20.5 ($\underline{C}D_3$), 28.4 (Me-gem),

29.0 (Cq-8), 41.7 (C-4), 41.8 (C-7), 91.9 (C-3, C-5), 93.0 (C-1), 169.9 (Me$\underline{C}$O). ESI MS: 303 ([*M*K]$^+$, 12), 287 ([*M*Na]$^+$, 100). **15-d6**: ^{1}H NMR: 1.23 (3H, s, Me-a), 1.40 (3H, s, Me-b), 1.81 (1H, dd, $J=3.0$, 13.7, H-7a), 1.87 (1H, t, $J=13.7$, H-7b), 2.08–2.24 (1H, m, H-4), 5.31 (1H, bs, H-1), 6.49 (1H, d, $J=2.9$, H-3), 6.53 (1H, d, $J=2.9$, H-5). ^{13}C NMR: 20.5 and 20.7 ($\underline{C}D_3$), 28.0, 30.6 (Me-b), 30.7 (Me-a), 41.3 (C-7), 41.6 (C-4), 91.2 (C-5), 91.6 (C-3), 93.9 (C-1), 169.5 (Me$\underline{C}$O), 170.2 (Me$\underline{C}$O). ESI MS: 287 ([*M*Na]$^+$, 100).