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Increased formation of oxepanes in non-aqueous medium in the cycloaddition of 3-*O*-allyl-1,2-isopropylidenefuranose *N*-Ph nitrones

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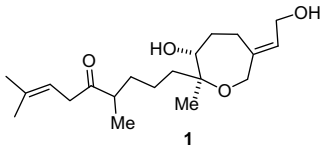
Abstract

Cycloaddition of 3-*O*-allyl-1,2-isopropylidene *N*-Ph nitrones afforded appreciably increased yields of oxepanes compared to the corresponding *N*-Me or *N*-Bn nitrones. Higher yields permitted some useful further transformations of the oxepanes.

Intramolecular cycloaddition of nitrones generated from *O*-alkenyl carbohydrate derivatives proved to be an efficient and operationally simple method for the synthesis of chiral cyclic ethers.[1–4] Five- to seven-membered oxacycles are obtained in good to excellent yields by the application of this strategy.[4–6] The 3-*O*-allylcarbohydrate nitrone cycloaddition (3-OACNC) strategy is particularly useful for accessing chiral pyran and oxepane derivatives.[4] The 3-OACNC strategy should be applicable to the synthesis of naturally occurring oxepanes such as zoapatanol (**1**).



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It was observed that the cycloaddition of the acyclic *N*-benzyl or *N*-methyl nitrones prepared from 3-*O*-allyl pyranose derivatives mainly afforded pyran derivatives.[4–6] In contrast, *N*-benzyl or *N*-methyl 3-*O*-allyl nitrones generated from 1,2-isopropylidene furanoses gave rise to oxepanes in the majority of cases.[4] Substitution at the allyl terminus or at 3-C of the furanose ring affected the regioselectivity such that oxepanes were either formed in poor yields or not at all.[4,6–8] This is why it is essential to explore how the regioselectivity of the 3-OACNC can be substantially altered in favour of oxepanes. The regioselectivity of the cycloaddition of *N*-benzyl or *N*-methyl nitrones was explained on the basis of the dependence of the transition states on steric factors.[4,6,8] Interestingly, a recent study by Chatterjee and Bhattacharya[9] described the formation of oxepanes as exclusive products via cycloaddition of the *N*-Ph nitrones of some of the earlier reported 3-*O*-allyl-1,2-isopropylidene derivatives in water in the presence of surfactants. Notwithstanding the desirability of aqueous reaction media, it is also necessary to investigate whether the reactions can be performed efficiently in non-aqueous media as well, as to date the majority of synthetic exercises involving natural products have employed organic solvents. It appeared a worthwhile task to investigate whether the use of a nitrone, in which the nitrone N-substituent can interact electronically with the nitrone, could influence the regioselectivity of the 3-OACNC reaction performed in organic solvents in such a manner as to favour the formation of oxepanes. An *N*-phenyl nitrone was expected to fulfil this requirement, because the aromatic ring would electronically interact with the nitrone dipole. Herein, we report that cycloaddition of the *N*-Ph analogs of some of the previously reported *N*-Bn and *N*-Me 1,2-isopropylidene-furanose nitrones in organic solvents indeed led to drastic

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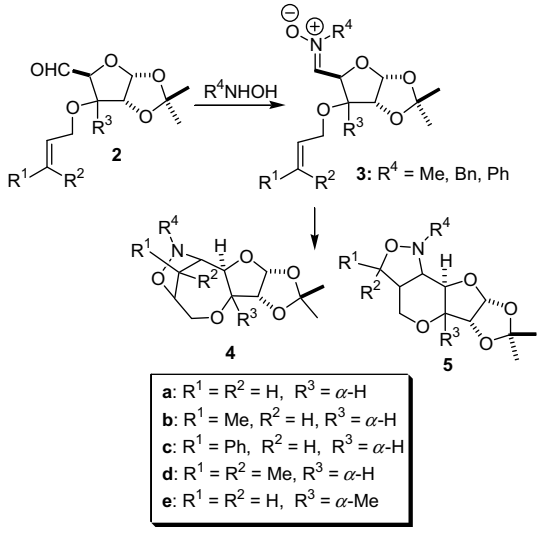
changes in the regioselectivity making available oxepanes, which have not been previously reported from other nitrones, or were obtained, in poorer yields.

Several 3-*O*-allyl/crotyl/prenyl/cinnamyl-1,2-isopropylidene furanose aldehydes **2** were prepared by known procedures.[3,8] The corresponding *N*-Ph nitrones **3** were then generated by reaction with *N*-PhNHOH in benzene in the presence of 3 Å molecular sieves (Scheme 1). Cycloaddition of these nitrones was performed, and the products were isolated by column chromatography. Comparison of the results of these cycloadditions performed in organic solvents with those previously reported is presented in Table 1.[10,11] The cycloaddition of the *N*-Ph nitrone of **3a** (**3a-*N*-Ph-nitrone**) gave rise to oxepane **4a**[9] as the major product (68%) along with traces (<5%) of the pyran **5a** (Scheme 2), the result being similar to that observed for the corresponding *N*-Me and *N*-Bn nitrones (Table 1).[4,6] Cycloaddition in aqueous medium in the presence of surfactants reportedly led to a higher yield of **4a**.[9] A striking effect of the introduction of Ph on the nitrone functionality was observed in the case of the cycloaddition of the 3-*O*-crotyl-*N*-Ph-nitrone (**3b-*N*-Ph-nitrone**), oxepane **4b**[9] being obtained in 54% yield along with a 16% yield of an inseparable 2:1 mixture of two diastereomeric pyrans **5b** (Scheme 2). The corresponding *N*-Bn nitrone was reported to give an 11% yield of the *N*-Bn analog of **4b** and a 2:1 diastereomeric mixture of the *N*-Bn analog of **5b** in 51% yield,[4] while the *N*-Me nitrone gave exclusively a 9:1 diastereomeric mixture of the *N*-Me analog of **5b**.[8] The particular efficacy of *N*-Ph-nitrone for driving the regioselectivity towards the oxepane was also prominent in the cycloaddition of the 3-*O*-cinnamyl-*N*-Ph nitrone (**3c-*N*-Ph-nitrone**) giving rise to the oxepane **4c** in 32% yield. The result was all the more significant, because the cycloaddition of the corresponding *N*-Me nitrone was reported to afford exclusively the *N*-Me analog of pyran **5c**,[8] which was also obtained from **3c-*N*-Ph-nitrone** in 35% yield (Scheme 2). The structure of **4c** was established on the basis of HSQC, HMBC, COSY and NOESY analysis. The absence of any multiplet at around δ 3.0 in the ^{1}H NMR spectrum of **4c** indicated the presence of the oxepane skeleton, as H-5 of pyran **5c** appeared as a multiplet at δ 2.98. The bridgehead proton H-5 of **4c** appeared as a singlet at δ 4.32 indicating

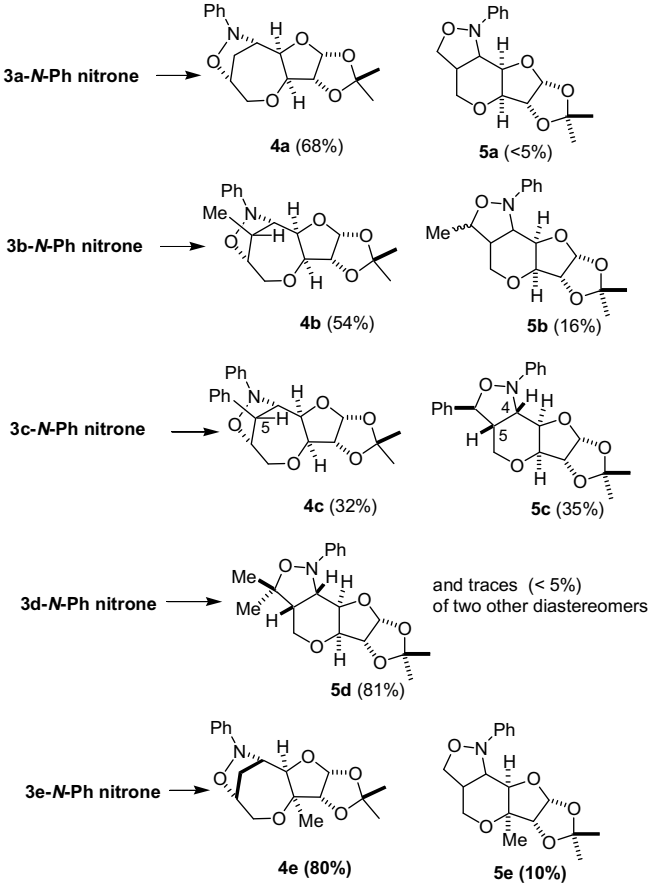


Scheme 1. General strategy for the generation and cycloaddition of 3-*O*-allyl-1,2-isopropylidene *N*-Me/Bn/Ph nitrones.

Table 1
Comparison of oxepane and pyran yields from *N*-Me, *N*-Bn, *N*-Ph nitrones

Nitrone[a]	% Oxepane[b] **4**	% Pyran[b] **5** (no. of diast.)	Ref.
3a-*N*-Me-nitrone	64	6 (1)	7
3a-*N*-Bn-nitrone	56	<5 (1)	4
3a-*N*-Ph-nitrone	68	<5 (1)	
3b-*N*-Me-nitrone		66 (2)	8
3b-*N*-Bn-nitrone	11	51 (2)	4
3b-*N*-Ph-nitrone	54	16 (2)	
3c-*N*-Me-nitrone		61 (1)	8
3c-*N*-Ph-nitrone	32	35 (1)	
3d-*N*-Bn-nitrone		70 (2)	4
3d-*N*-Ph-nitrone		81 (1)	
3e-*N*-Me-nitrone	38	30 (3)	4
3e-*N*-Bn-nitrone	50		4
3e-*N*-Ph-nitrone	80	10 (1)	

[a] The preparation of *N*-Ph nitrones is described in Ref. 10.
[b] Spectral data for new oxepanes and pyrans are presented in Ref. 11.

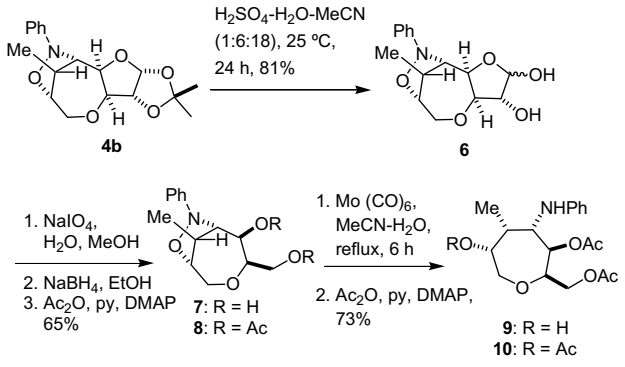


Scheme 2. Cycloadditions of 1,2-isopropylidenefuranose *N*-Ph nitrones.

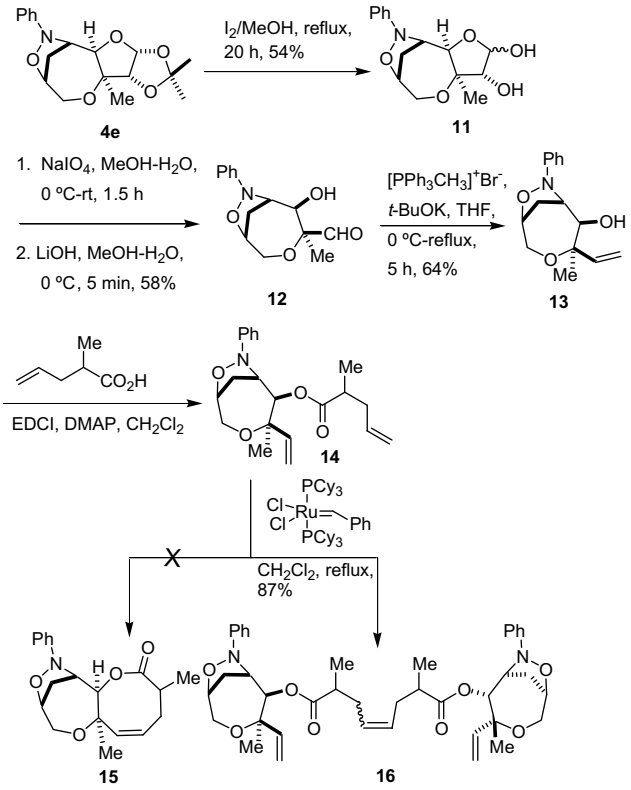
the absence of any vicinal coupling with the adjacent bridgehead protons due to the occurrence of 90° dihedral angles between the coupling protons, which was also supported by molecular modelling. The cycloaddition of the 3-*O*-prenyl-*N*-Ph nitrone (**3d-*N*-Ph-nitrone**) gave rise to pyran **5d**[9] as an exclusive product, as was observed in the case of the corresponding *N*-Bn nitrone.[4] The most striking effect of the use of the *N*-Ph-nitrone was observed in the cycloaddition of **3e-*N*-Ph-nitrone** which afforded the oxepane **4e** in 80% yield (Scheme 2). The corresponding *N*-Me and *N*-Bn nitrones reportedly gave 38% and 50% yields of the analogous oxepanes (Table 1).[4] Moreover, a single pyran diastereomer **5e** was obtained in 10% yield, whereas three diastereomeric pyrans were formed in 30% yield in the cycloaddition of the corresponding *N*-Me nitrone.[4] The stereochemistry of **4e** was based on analogy with those of the known *N*-Me and *N*-Bn analogs.[4] The substantially increased formation of **4e** was significant because of its potential use as a precursor in the synthesis of zoapatanol (**1**).

The reason for the pronounced change in the regioselectivity of the cycloaddition of the *N*-Ph nitrones has not been investigated in this study. It is probable that the presence of the Ph group on the nitrone moiety changed the frontier orbital coefficients in such a way as to favour the formation of oxepanes to a greater extent than the corresponding *N*-Me or *N*-Bn nitrones. In the latter cases, steric factors primarily influenced the regioselectivity.[4,6,8] Despite the absence of an adequate theoretical study directed towards the explanation of the regioselectivity, the dramatic effect of the *N*-Ph nitrone cannot be overlooked in the above cycloadditions.

Formation of oxepanes in substantially higher yields in some of the cycloadditions would permit their use in future synthetic exercises. In order to demonstrate this possibility, oxepane **4b** was converted to the enantiomerically pure pentasubstituted oxepane **10** as outlined in Scheme 3. Removal of the isopropylidene protecting group by treatment with aq H_2SO_4 gave diol **6** as an anomeric mixture. Vicinal diol cleavage by $NaIO_4$ followed by the reduction of the resulting hydroxyaldehyde gave **7** and subsequent acetylation afforded the oxepane derivative **8** (Scheme 3).



Scheme 3. Conversion of **4b** to pentasubstituted oxepane **10**.



Scheme 4. Attempted conversion of **4e** to an intermediate **15** of zoapatanol.

Treatment of **8** with $Mo(CO)_6$ led to the formation of aminoalcohol **9**, which on acetylation gave rise to the pentasubstituted oxepane **10** in 73% yield. Under the conditions employed, the aniline moiety did not undergo acetylation. Another example is outlined in Scheme 4. Removal of the isopropylidene protection in **4e** by treatment with I_2 followed by the conversion of the resulting diol **11** to hydroxyaldehyde **12** with $NaIO_4$ and subsequent Wittig reaction led to the formation of the vinyl oxepane **13**. Attempted ring closing metathesis of the dienic ester **14** prepared from **13** and (±)2-allyl propionic acid failed to afford lactone **15**, which was envisaged as a precursor for zoapatanol (**1**). Instead, the cross metathesis product **16** (mixture of *E*/*Z* and other diastereomers) was obtained in 87% yield (Scheme 4).

In conclusion, the work described herein has demonstrated that the yields of oxepanes in the nitrone cycloaddition of 3-*O*-allyl-1,2-isopropylidenefuranose derivatives could be significantly increased in non-aqueous medium by switching to *N*-Ph nitrones. Higher yields of oxepanes would permit the use of these intermediates in future synthetic exercises. Work in this direction is currently underway.

Acknowledgements

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References and notes

1. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
2. Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419.
3. Frederickson, M. *Tetrahedron* **1997**, *53*, 403.
4. Bhattacharjee, A.; Datta, S.; Chattopadhyay, P.; Ghoshal, N.; Kundu, A. P.; Pal, A.; Mukhopadhyay, R.; Chowdhury, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron* **2003**, *59*, 4623. and references cited therein.
5. Ghorai, S.; Mukhopadhyay, R.; Kundu, A. P.; Bhattacharjya, A. *Tetrahedron* **2005**, *61*, 2999.
6. Shing, T. K. M.; Zhong, Y.-L. *Tetrahedron* **2001**, *57*, 1573.
7. Shing, T. K. M.; Fung, W.-C.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1994**, 449.
8. Sharma, G. V. M.; Reddy, K. R.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 8893.
9. Chatterjee, A.; Bhattacharya, P. K. *J. Org. Chem.* **2006**, *71*, 345.
10. *General experimental procedure for nitrone cycloaddition.* A solution of the aldehyde **2** (1.5 mmol) and PhNHOH (2.2 mmol) in benzene (12 ml) containing 3 Å molecular sieves (2.5 g) was heated at reflux for 5 h. The mixture was then filtered, and the residue obtained after removal of the solvent from the filtrate was chromatographed over Si-gel (100–200 mesh) to afford the products.
11. *Physical data for new compounds.* Compound **4c**: $[\alpha]_D$ −150.1 (*c* 0.31, $CHCl_3$); IR (neat): 2938, 1594, 1491, 1452, 1376, 1298, 1214, 1150, 1089, 1021, 856, 756, 698 cm^{-1}; MS (ESI): *m/z* 418 (M^++Na); ^1H NMR ($CDCl_3$, 600 MHz): δ 1.33 (s, 3H), 1.47 (s, 3H), 3.83 (d, $J = 13.2$ Hz, 1H), 3.94 (dd, $J = 13.2$, 4.2 Hz, 1H), 4.20 (br s, 1H), 4.31 (m, 1H), 4.32 (s, 1H), 4.48 (d, $J = 4.2$ Hz, 1H), 4.52 (d, $J = 3.6$ Hz, 1H), 4.84 (d, $J = 4.2$ Hz, 1H), 6.03 (d, $J = 3.6$ Hz, 1H), 6.83 (t, $J = 7.2$ Hz, 1H), 6.93 (d, $J = 7.8$ Hz, 2H), 7.11 (m, 7H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 26.2 (CH_3), 26.6 (CH_3), 47.2 (CH), 70.2 (CH), 72.7 (CH_2), 77.4 (CH), 83.0 (CH), 83.1 (CH), 84.4 (CH), 104.7 (CH), 111.9 (q), 113.8 (CH), 121.0 (CH), 126.5 (CH), 127.8 (CH), 128.2 (CH), 128.7 (CH), 140.7 (q), 149.5 (q). HRMS: calcd for *m/z*: $C_{23}H_{25}NO_5Na$, 418.1630. Found: 418.1667; Compound **5c**: mp 145–146 °C; $[\alpha]_D$ −160.1 (*c* 0.43, $CHCl_3$); IR (KBr): 2907, 1596, 1490, 1380, 1265, 1215, 1163, 1085, 882, 758, 697 cm^{-1}; MS (ESI): *m/z* 418 (M^++Na); ^1H NMR ($CDCl_3$, 600 MHz): 1.31 (s, 3H), 1.43 (s, 3H), 2.98 (m, 1H), 3.77 (dd, $J = 12.0$, 10.2 Hz, 1H), 3.87 (d, $J = 6.6$ Hz, 1H), 4.04 (dd, $J = 12.0$, 6.0 Hz, 1H), 4.19 (d, $J = 2.4$ Hz, 1H), 4.23 (br s, 1H), 4.58 (d, $J = 3.6$ Hz, 1H), 4.91 (d, $J = 3.6$ Hz, 1H), 5.88 (d, $J = 3.6$ Hz, 1H), 7.13 (t, $J = 7.2$ Hz, 1H), 7.24–7.29 (m, 7H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): 26.1 (CH_3), 26.7 (CH_3), 46.6 (CH), 60.6 (CH), 64.8 (CH_2), 73.0 (CH), 77.2 (CH), 81.0 (CH), 84.3 (CH), 104.3 (CH), 111.8 (q), 118.7 (CH), 124.4 (CH), 126.2 (CH), 128.0 (CH), 128.6 (CH), 129.0 (CH), 139.5 (q), 148.9 (q). Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.62; H, 6.65; N, 3.27. Compound **4e**: $[\alpha]_D$ −194.7 (*c* 0.65, $CHCl_3$); IR (neat): 2986, 2938, 1593, 1487, 1447, 1376, 1260, 1214, 1165, 1080 cm^{-1}; MS (ESI): *m/z* 356 (M^++Na); ^1H NMR ($CDCl_3$, 600 MHz): δ 1.35 (s, 3H), 1.58 (s, 3H), 1.61 (s, 3H), 1.91 (m, 1H), 2.58 (d, $J = 12.1$ Hz, 1H), 3.56 (dd, $J = 13.2$, 3.6 Hz, 1H), 4.01 (d, $J = 13.2$ Hz, 1H), 4.20 (d, $J = 3.6$ Hz, 1H), 4.20–4.24 (m, 2H), 4.70 (dd, $J = 9.0$, 3.6 Hz, 1H), 5.89 (d, $J = 3.6$ Hz, 1H), 6.97–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 12.8 (CH_3), 26.4 (CH_3), 26.5 (CH_2), 27.2 (CH_3), 67.4 (CH), 67.6 (CH_2), 78.8 (CH), 81.7 (CH), 85.4 (q), 88.4 (CH), 103.7 (CH), 112.0 (q), 115.6 (CH), 122.6 (CH), 128.8 (CH), 152.2 (q). Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.93; H, 6.72; N, 4.46. Compound **5e**: $[\alpha]_D$ −238.3 (*c* 0.13, $CHCl_3$); IR (neat): 2983, 2933, 1595, 1489, 1455, 1376, 1216, 1165, 1096 cm^{-1}; MS (ESI): *m/z* 356 (M^++Na); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 3H), 1.51 (s, 3H), 1.54 (s, 3H), 2.92 (m, 1H), 3.75 (d, $J = 8.6$ Hz, 1H), 3.83–3.93 (m, 4H), 4.21 (br s, 1H), 4.28 (d, $J = 3.5$ Hz, 1H), 5.88 (d, $J = 3.6$ Hz, 1H), 7.00 (t, $J = 7.2$ Hz, 1H), 7.09 (d, $J = 7.8$ Hz, 2H), 7.31 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2 (CH_3), 26.5 (CH_3), 27.2 (CH_3), 38.4 (CH), 60.5 (CH_2), 63.7 (CH), 69.4 (CH_2), 77.0 (CH), 79.7 (q), 87.4 (CH), 104.4 (CH), 112.2 (q), 114.9 (CH), 122.3 (CH), 129.1 (CH), aromatic quaternary C is not visible. HRMS: calcd for $C_{18}H_{23}NO_5Na$, *m/z*: 356.1474. Found: 356.1486. Compound **10**: $[\alpha]_D$ +43.1 (*c* 0.31, $CHCl_3$); MS (ESI): *m/z* 416 (M^++Na); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.09 (d, $J = 7.2$ Hz, 3H), 2.03 (s, 3H), 2.15 (s, 3H), 2.18 (s, 3H), 2.55 (m, 1H), 3.67 (dd, $J = 13.5$, 5.7 Hz, 1H), 3.85 (dd, $J = 5.5$, 1.9 Hz, 1H), 3.96 (m, 1H), 4.19–4.29 (m, 3H), 5.20 (m, 1H), 5.33 (m, 1H), 6.74 (m, 2H), 7.21 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.6 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 33.3 (CH), 58.5 (CH), 62.3 (CH_2), 69.6 (CH_2), 72.6 (CH), 76.3 (CH), 77.2 (CH), 112.7 (CH), 117.8 (CH), 129.6 (CH), 147.3 (q), 169.7 (q), 170.2 (q), 170.7 (q). HRMS: calcd for $C_{18}H_{23}NO_5Na$, *m/z*: $C_{20}H_{27}NO_7Na$, 416.1685. Found: 416.1706. Compound **14**: $[\alpha]_D$ −153.4 (*c* 0.35, $CHCl_3$); IR (neat): 1731, 1640, 1596 cm^{-1}; MS (EI): *m/z* 357 (M^+); ^1H NMR($CDCl_3$, 300 MHz; mixture of diastereomers due to C–CH_3): δ 1.15–1.17 (m, 3H), 1.64 (s, 3H), 1.97–2.01 (m, 1H), 2.17–2.22 (m, 1H), 2.43 (m, 1H), 2.56–2.68 (m, 2H), 3.76 (dd, $J = 13.8$, 3.4 Hz, 1H), 3.98–4.09 (m, 2H), 4.77–4.80 (m, 1H), 4.97–5.14 (m, 4H), 5.26 (d, $J = 17.2$ Hz, 1H), 5.72–5.83 (m, 2H), 6.83–7.56 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.0 (CH_3), 20.8 (CH_3), 27.7 (CH_3), 37.9 (CH_2), 38.2 (CH_2), 39.6 (CH), 39.7 (CH), 68.6 (CH_2), 69.0 (CH), 69.1 (CH), 76.7 (CH), 76.9 (CH), 79.6 (CH), 79.7 (CH), 80.3 (q), 112.1 (CH_2), 112.2 (CH_2), 115.9 (CH), 117.3 (CH_2), 118.0 (CH), 122.8 (CH), 129.1 (CH), 135.8 (CH), 137.9 (CH), 143.3 (CH), 143.4 (CH), 143.5 (CH), 152.5 (q), 175.6 (q), 175.7 (q). Compound **16**: IR (neat): 1730, 1646, 1596 cm^{-1}; MS (FAB): *m/z* 687 (M^++H), 709 (M^++Na); ^1H NMR ($CDCl_3$, 300 MHz; as a mixture of *E*/*Z* and diastereomers due to C–CH_3): δ 1.04–1.06 (m, 6H), 1.60–1.63 (m, 6H), 1.98–2.51 (m, 8H), 2.63 (dd, $J = 11.9$, 4.6 Hz, 2H), 3.76 (d, $J = 13.8$ Hz, 2H), 3.95–4.09 (m, 4H), 4.77 (m, 2H), 4.97–5.12 (m, 4H), 5.22–5.36 (m, 4H), 5.76–5.85 (m, 2H), 6.82–7.55 (m, 10H).