# Enantioselective Reduction of Benzofuranyl Aryl Ketones

Ian Carpenter, Matthew L. Clarke*

School of Chemistry, University of St Andrews, EaStCHEM, St. Andrews, Fife, KY16 9ST, UK
Fax +44(1334)463008; E-mail: mc28@st-andrews.ac.uk

*Received 27 August 2010*

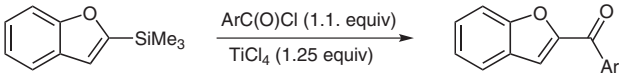
**Abstract:** Enantioselective transfer hydrogenation of benzofuranyl aryl ketones proceeds with moderate to good enantioselectivity even when the aryl group is not sterically differentiated by *ortho*-substituents. The best results are obtained with substrates that are functionalised by electron-withdrawing aryl groups that contrast with the electron-rich benzofuran, which is consistent with [Ru–ArC–H]·Ar π interactions acting as a control element. Enantioselective pressure hydrogenation gives lower enantioselectivity irrespective of electronic effects, unless the aryl group is *ortho*-substituted, in which case up to 86% ee can be realised.

**Key words:** asymmetric transfer hydrogenation, asymmetric hydrogenation, heterocyclic ketones, asymmetric catalysis, electronic control

Asymmetric hydrogenation and transfer hydrogenation of aryl alkyl ketones is now the preferred technology for the synthesis of enantiomerically enriched aryl-substituted secondary alcohols.[1] Many drugs and natural products can be synthesised from heteroaryl secondary alcohols.[2] Although not exhaustively investigated, some studies have shown that acetyl-substituted heterocycles can also take part in these asymmetric reductions with good to excellent enantioselectivity. Most relevantly, several publications establish that alkyl benzofuranyl ketones such as 2-acetylbenzofuran can be reduced with high enantioselectivity.[3] A project on heterocycle hydrogenation led us to require secondary alcohols flanked with benzofuran and aryl substituents. There do not appear to be any studies dealing with asymmetric transfer hydrogenation of benzofuranyl aryl ketones. Since benzofuranyl and dihydrobenzofuranyl heterocycles, including benzofuranyl aryl alcohols are found in several classes of drugs and biologically active compounds,[3,4] a study dedicated to asymmetric reduction of benzofuranyl ketones seemed somewhat overdue. In addition to the synthetic uses of such alcohols, we were also intrigued by the implications for selectivity that arise when the C=O bonds are flanked by two electronically different aromatic substituents.

The most relevant studies in the literature for comparative purposes are the hydrogenation of aryl aryl ketones. In pressure hydrogenation, reduction of aryl aryl ketones proceeds with poor to moderate enantioselectivity (8–47% ee),[5b] unless (only) one of the aryl groups is *ortho*-substituted. Somewhat higher ee values have been realised in pressure hydrogenation of pyridyl aryl ketones (14–78% ee).[6] Transfer hydrogenation of 4-cyano-4′-methoxybenzophenone proceeds with 33% ee using [RuCl(NH^O)($C_6H_6$)] type catalysts;[5a] it is proposed that an enhanced ArC–H·Ar π interaction between the Ru-benzene moiety and the electron-donating aryl ring contributes to this moderate selectivity. We speculated that the slightly different shape, combined with the electron-rich character of benzofuran, could lead to an asymmetric reduction of benzofuranyl aryl ketones even if they were not strongly differentiated by *ortho* substituents. Here, we report an investigation into the asymmetric transfer hydrogenation of benzofuranyl aryl ketones and compare the selectivities observed to those found using pressure hydrogenation.

The desired ketones were prepared by a slight modification of the method reported by Gill,[7] using 2-trimethylsilylbenzofuran and a range of acid chlorides (Scheme 1). Significantly improved yields were found using these aromatic acid chlorides compared with the attempt at benzoylation reported by Gill.[7]



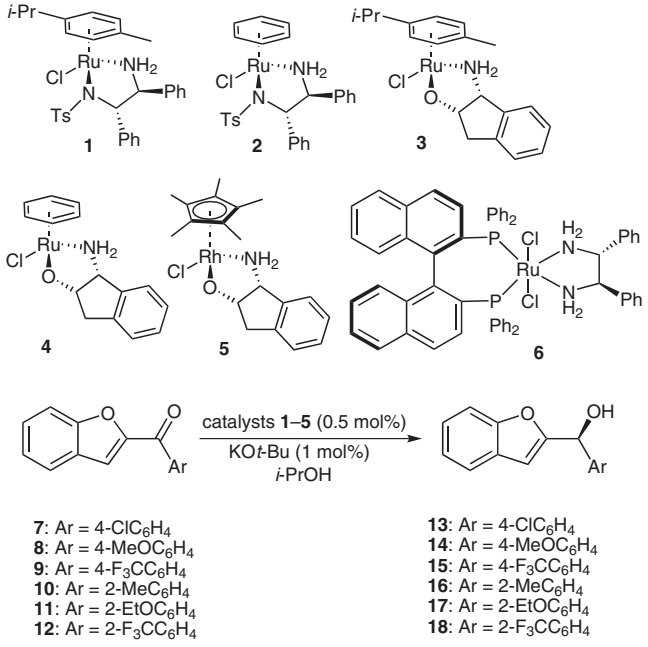

**7**: Ar = 4-$ClC_6H_4$, commercial
**8**: Ar = 4-$MeOC_6H_4$ (67%)
**9**: Ar = 4-$F_3CC_6H_4$ (25%)
**10**: Ar = 2-$MeC_6H_4$ (66%)
**11**: Ar = 2-$EtOC_6H_4$ (78%)
**12**: Ar = 2-$F_3CC_6H_4$ (49%)

**Scheme 1**

Typical transfer hydrogenation catalysts employed in this study are pictured in Scheme 2. These catalysts were prepared in situ since there is ample precedent that this results in formation of the complexes **1**–**5**.[1] The Noyori pressure hydrogenation catalyst was synthesised by a literature method.[1h] Sodium borohydride reductions were carried out for each ketone for the purpose of developing a suitable analytical method. The transfer hydrogenation of ketones **7**–**12** was examined using five of the state-of-the-art catalyst systems as shown in Scheme 2.

The results, which are summarised in Table 1, show that there was significant enantioselectivity in the hydrogenation of *para*-substituted benzofuranyl aryl ketones, with significantly better enantioselectivity being observed when the *para*-substituent was electron-withdrawing (compare Table 1, entries 6–10 with entries 1–5 and 11–15).

*SYNLETT* 2011, No. 1, pp 0065–0068
Advanced online publication: 07.12.2010
DOI: 10.1055/s-0030-1259080; Art ID: D23010ST




**Scheme 2** Asymmetric reduction catalysts and the asymmetric reduction of benzofuranyl aryl ketones

Kinetic investigations were outside the scope of this study, but it is clear from the conversions that the rhodium catalysts are more active in these reductions. In the case of the *o*-tolyl ketone **10**, the substrate is reduced more sluggishly, at least with catalysts **1**–**4**, and high conversions are not reached (Table 1, entries 16–19). This is not an issue for the rhodium catalyst since high conversion and moderately high enantioselectivity can be achieved (entry 20). Asymmetric transfer hydrogenation of ketones **11** and **12** was especially challenging, with no conversion being realised at 40 °C, and low conversions being achieved at 80 °C for catalysts **1**–**4** (entries 21–24 and 26–29). Catalyst **5** did reduce these ketones at 80 °C and, in the case of **12**, 75% conversion and 76% ee could be realised.

There seems to be a consensus that enantioselection in transfer hydrogenation is under significant electronic control as a result of arene·H–CAr–Ru interactions, and the results obtained here support this. This is somewhat less clear in the case of pressure hydrogenation.[5b,c] We therefore carried out pressure hydrogenation of these substrates using [$RuCl_2$(*R*-BINAP)(*R*,*R*-DPEN)] with the results shown in Table 2.

The selectivity pattern for these catalysts is quite different. The *para*-substituted ketones all gave very similar enantioselectivities regardless of electronic effects, which is in contrast with the ~30% ee increase observed in the electron-withdrawing ketones using the Ru /Ts-DPEN catalysts. The *ortho*-substituted ketones **10**–**12** all gave significantly better enantioselectivity; the 86% ee value obtained using ketone **11**, which is of some practical val-

**Table 1** Asymmetric Reduction of Substituted Benzofuranyl Aryl Ketones[a]

| Entry | Catalyst[b] | Ketone | Temp (°C) | Conv. (%)[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **1** | **7** | 40 | 73 | 64 |
| 2 | **2** | **7** | 40 | 86 | 59 |
| 3 | **3** | **7** | 40 | 95 | 33 |
| 4 | **4** | **7** | 40 | 89 | 30 |
| 5 | **5** | **7** | 40 | >99 (97) | 47 |
| 6 | **1** | **8** | 40 | 46 | 55 |
| 7 | **2** | **8** | 40 | 71 | 32 |
| 8 | **3** | **8** | 40 | 87 | 26 |
| 9 | **4** | **8** | 40 | 59 | 29 |
| 10 | **5** | **8** | 40 | >99 (87) | 28 |
| 11 | **1** | **9** | 40 | >99 | 69 |
| 12 | **2** | **9** | 40 | 20 | 64 |
| 13 | **3** | **9** | 40 | >99 | 42 |
| 14 | **4** | **9** | 40 | 98 | 57 |
| 15 | **5** | **9** | 40 | >99 (98) | 55 |
| 16 | **1** | **10** | 40 | 0 | n.d. |
| 17 | **2** | **10** | 40 | 0 | n.d |
| 18 | **3** | **10** | 40 | 17 | 73 |
| 19 | **4** | **10** | 40 | 87 | 87 |
| 20 | **5** | **10** | 40 | >99 (99) | 74 |
| 21 | **1** | **11** | 80 | 7 | n.d. |
| 22 | **2** | **11** | 80 | 24 | 58 |
| 23 | **3** | **11** | 80 | 20 | 61 |
| 24 | **4** | **11** | 80 | 32 | 47 |
| 25 | **5** | **11** | 80 | 66[e] | 45 |
| 26 | **1** | **12** | 80 | 2 | n.d. |
| 27 | **2** | **12** | 80 | 12 | 52 |
| 28 | **3** | **12** | 80 | 36 | 53 |
| 29 | **4** | **12** | 80 | 16 | 25 |
| 30 | **5** | **12** | 80 | 75 (51) | 76 |

[a] Reactions performed in *i*-PrOH (3 mL) for 16 h.
[b] Catalysts formed in situ from 0.5% ligand and 0.25% of appropriate dimeric Ru or Rh species.
[c] Determined against an internal standard of $Et_4Si$. Isolated yields of product after chromatography given in brackets.
[d] Determined by HPLC.
[e] 99% yield obtained using 1% catalyst.

**Table 2** Pressure Hydrogenation Using Catalyst **6**[a]

| Entry | Ketone | Conv. (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | **7** | 89 | 44 |
| 2 | **8** | >99 | 48 |
| 3 | **9** | 83 | 42 |
| 4 | **10** | >99 | 83 |
| 5 | **11** | >99 | 86 |
| 6 | **12** | 77 | 81 |

[a] Reactions were carried out using catalyst **6** (0.5 mol%) at 40 °C and 50 bar hydrogen, 1% KO*t*-Bu in *i*-PrOH (3 mL) for 16 h.
[b] Conversion determined against $Et_4Si$ as internal standard.
[c] Determined by HPLC (see experimental section), and assigned as *R* configuration.

ue, is higher than observed in the reduction of the benchmark substrate acetophenone using this catalyst.

In conclusion, this study on the asymmetric reduction of some benzofuranyl aryl ketones provides support for the proposal that certain transfer hydrogenation catalysts have a significant element of electronic control over the selectivity, most likely as a result of favourable Ru–ArC–H·Ar π interactions in the transition state. On the other hand, the results are consistent with these pressure hydrogenations being primarily under steric control. This study also provides a convenient method to prepare secondary alcohols flanked with benzofuranyl and aryl substituents in good enantioselectivity.[9]

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## Acknowledgment

We thank the EPSRC for funding, Johnson Matthey for the loan of certain precious metal salts and all the technical staff in the School of Chemistry.

## References and Notes

(1) (a) *The comprehensive handbook of homogeneous hydrogenation*; Elsevier, C. J.; DeVries, J. N. H., Eds.; Wiley-VCH: Weinheim, **2006**. (b) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300. (c) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (d) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (e) Ohhuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417. (f) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.-I.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233. (g) Blacker, A. J.; Mellor, B. J. WO9842643A1, Priority date 26/3/1997 (Avecia)**, 1997**. (h) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kazawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1703.

(2) (a) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40. (b) Lennon, I. C.; Casy, G.; Johnson, N. B. *Chem. Today* **2003**, 63. (c) Lennon, I. C.; Moran, P. H. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 855. (d) Lennon, I. C.; Ramsden, J. A. *Org. Process Res. Dev.* **2005**, *9*, 110. (e) Diaz-Venezuela, M. B.; Phillips, S. D.; France, M. B.; Gunn, M. E.; Clarke, M. L. *Chem. Eur. J.* **2009**, *15*, 1227. (f) Chen, C.-Y.; Reamer, R.; Chilenski, J. R.; McWilliams, C. J. *Org. Lett.* **2003**, *5*, 5039. (g) Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749. (h) Morris, D. J.; Hayes, A. M.; Wills, M. *J. Org. Chem.* **2006**, *71*, 7035.

(3) (a) Wu, X.; Vinci, D.; Ikariya, T.; Xiao, J. *Chem. Commun.* **2005**, 447. (b) Zaidlewicz, M.; Tafelska-Kaczmarek, A.; Prewysz-Kwinto, A. *Tetrahedron: Asymmetry* **2005**, *16*, 3205.

(4) (a) Nichols, D. E.; Hoffman, A. J.; Oberlender, R. A.; Riggs, R. M. *J. Med. Chem.* **1986**, *29*, 302. (b) Cho, C.-H.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2008**, *10*, 941; and references therein. (c) Nichols, D. E.; Snyder, S. E.; Oberlender, R.; Hohnson, M. P.; Huang, Z. *J. Med. Chem.* **1991**, *34*, 276. (d) Johansson, G.; Brisander, N.; Sundquist, S.; Hacksell, U. *Chirality* **1998**, *10*, 813. (e) de Carvalho e Silveiria, G. P.; Coelho, F. *Tetrahedron Lett.* **2005**, *46*, 6477. (f) Sun, L.-Q.; Takaki, K.; Chen, J.; Bertenshaw, S.; Iben, L.; Mahle, C. D.; Ryan, E.; Gao, Q.; Xu, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1345. (g) Vinh, T. K.; Lopez Delgado, P. O.; Fernandez-Perez, S.; Walters, H. M.; Smith, H. J.; Nichols, P. J.; Simons, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2105.

(5) (a) Brandt, P.; Roth, P.; Andersson, P. G. *J. Org. Chem.* **2004**, *69*, 4885. (b) Ohhuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659. (c) Sandoval, C. A.; Qixun, S.; Liu, S.; Noyori, R. *Chem. Asian J.* **2010**, *4*, 1221.

(6) Maerten, E.; Agbossou-Niedercorn, F.; Castanet, Y.; Mortreux, A. *Tetrahedron* **2008**, *64*, 8700.

(7) Gill, M. *Tetrahedron* **1984**, *40*, 621.

(8) An almost identical *R*-configured alcohol to **13** (fluoro rather than chloro) gave opposite optical rotation to (*S*)-**13**, see: Botta, M.; Summa, V.; Corelli, F.; Di Pietro, G.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263.

(9) The catalysts used were formed from either $[RuCl_2(benzene)]_2$, $[RuCl_2(p\text{-cymene})]_2$ or $[RhCl_2Cp^*]_2$ and (*S*,*S*)-Ts-DPEN or (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol. Using $[RuCl_2(R)$-BINAP(*R*,*R*)-DPEN], alcohol **16** was assigned as having *R*-configuration by Mosher analysis[6,8] on the mandelate ester (see the Supporting Information). A similar analysis was carried out on alcohol **15**. The other alcohols, which show similar HPLC behaviour, are therefore proposed to have the (*R*)-configuration. Transfer hydrogenation reactions using $[RuCl_2(benzene)]_2$, $[RuCl_2(p\text{-cymene})]_2$ or $[RhCl_2Cp^*]_2$ combined with (*S*,*S*)-Ts-DPEN or (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol as catalyst, gave the opposite *S*-configured alcohols in each case.

**2-(Trimethylsilyl)benzofuran**:[7] A solution of 2,3-benzofuran (5.1 mL, 46 mmol) in anhydrous THF (50 mL) was cooled to –78 °C in a nitrogen atmosphere. *n*-BuLi (40 mL, 1.6 M in hexanes, 64 mmol) was then added slowly to the solution. After stirring at –78 °C for 1 h, chlorotri-methylsilane (9.5 mL, 75 mmol) was added to the suspension. The mixture was then allowed to stir at –78 °C for 1 h, then at r.t. for a further 16 h. The reaction mixture was diluted with hexanes, filtered, and evacuated in vacuo to give a crude yellow oil (9.108 g). The crude product was purified by column chromatography (silica, hexane), to give a colourless oil (7.368 g, 39 mmol, 84%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.34 (s, 9 H, $SiCH_3$), 6.84 (s, 1 H, C*H*C$SiMe_3$), 7.13–7.29 (m, 2 H, 2 × ArH), 7.45–7.60 (s, 2 H, 2 × ArH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 0.1 [$Si(CH_3)_3$], 113.1 [*C*HC($SiMe_3$)],

117.8 (Ar*C*H), 122.8 (Ar*C*H), 124.1 (Ar*C*H), 126.1 (Ar*C*H), 129.8 (Ar*C ipso*-CH), 159.9 (*C*SiMe$_3$), 165.3 (Ar*C ipso*-Oxygen); MS (ES+): *m*/*z* = 213.12 [M + Na]$^+$.

**Acylation of 2-(trimethylsilyl)benzofuran; General Procedure A:** To a solution of an acid chloride (1.1 equiv) in anhydrous $CH_2Cl_2$ under a nitrogen atmosphere, trimethylsilylbenzofuran (1.0 equiv) was added. The solution was stirred vigorously at r.t., whilst $TiCl_4$ (1.25 equiv) was added dropwise. The resulting suspension was stirred at r.t. for 48 h, followed by addition of water. The solution was extracted with $Et_2O$, dried, and concentrated in vaccuo to give the crude product. The crude product was purified by column chromatography (hexane–$CH_2Cl_2$).

**Using general Procedure A**: Using trimethylsilylbenzofuran (5.00 g, 26.3 mmol), 2-methoxybenzoyl chloride (4.39 g, 28.5 mmol), and $TiCl_4$ (3.6 mL, 33.2 mmol) in $CH_2Cl_2$ (100 mL), ketone **10** was obtained as a pale-yellow oil (4.10 g, 17.4 mmol, 66%). $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, $CH_3$), 7.26–7.33 (m, 4 H, 4 × ArH), 7.40–7.45 (m, 1 H, ArH), 7.46–7.51 (m, 1 H, ArH), 7.56 (m, 1 H, ArH), 7.62 (d, 1 H, ArH), 7.60–7.64 (m, 1 H, ArH), 7.66–7.69 (m, 1 H, ArH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 20.2 ($CH_3$), 113.2 (*C*HCC=O), 117.9 (Ar*C*H), 123.9 (Ar*C*H), 124.4 (Ar*C*H), 125.7 (Ar*C*H), 127.5 (Ar*C ipso*-CH), 128.9 (Ar*C*H), 129.0 (Ar*C*H), 131.4 (Ar*C*H), 131.7 (Ar*C*H), 137.8 (Ar*C*), 153.1 (O*C*C=O), 156.7 (Ar*C ipso*-Oxygen), 187.4 (*C*=O); MS (ES+): *m*/*z* = 258.85 [M + Na]$^+$; HRMS: *m*/*z* calcd. for $C_{16}H_{12}O_2Na$: 259.0735; found: 259.0732; IR: 3064, 1939, 1660, 1549,1445, 1328, 1219, 1186, 1114cm$^{-1}$; Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.39; H, 5.05.

**Transfer Hydrogenation; General Procedure B:** Under a nitrogen atmosphere, the substrate, internal standard, 0.25 mol% metal complex, 0.5 mol% ligand and *t*-BuOK (1 M in *t*-BuOH) were transferred into a microwave vial and dissolved in anhydrous and degassed solvent (3 mL) and stirred for 2 min. The reaction was then heated and stirred for16 h. The vials were cooled and the crude reaction mixture was analysed by $^1$H NMR using tetraethylsilane as an internal standard to calculate the conversion into product. In some instances, the products were isolated using column chromatography, and the products were fully characterised.

**Pressure Hydrogenation; General Procedure C:** Under a nitrogen atmosphere, the substrate, internal standard, 0.25 mol% metal complex and 0.5 mol% ligand were transferred into a microwave vial and dissolved in anhydrous and degassed solvent (3 mL) and stirred for 2 min. The vials were then transferred to a steel autoclave and pressurised with $H_2$ gas. The reaction was then heated and stirred for 16 h. The autoclave was immersed in cold water and depressurised. The crude reaction mixture was then analysed by $^1$H NMR using tetraethylsilane as an internal standard to calculate the conversion into product.

**(*S*)-*o*-Methylphenyl(benzofuran-2-yl)methanol (16):** Using general procedure B with substrate (58.3 mg, 0.23 mmol), [RhCp*Cl$_2$]$_2$ (0.25 mol%), and aminoindanol (0.5 mol%), a yellow semi-solid was obtained (69 mg, 0.228 mmol, 99%, >99% conversion, 74% *ee* [determined by HPLC: OD-H (*i*-PrOH–hexane, 10:90; flow: 0.5 mL/min)]). Comparison of the HPLC behaviour of this compound to an analogous sample that had been treated with methoxyphenylacetic acid and analysed by NMR, showed this sample to have (*S*)-configuration. $[\alpha]_D^{20}$ +28.2 (*c* = 2.2 g/100 mL, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, $CH_3$), 2.42 (br s, 1 H, OH), 6.07 (s, 1 H, C*H*OH), 6.34 (s, 1 H, ArH), 7.08–7.24 (m, 5 H, 5 × ArH), 7.35–7.45 (m, 2 H, 2 × ArH), 7.46–7.53 (m, 1 H, ArH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 19.1 ($CH_3$), 67.5 (CHOH), 104.6 (Ar*C*H), 111.5 (*C*HCC=O), 121.3 (Ar*C*H), 122.7 (Ar*C*H), 124.5 (Ar*C*H), 126.3 (Ar*C*H), 128.4 (Ar*C ipso*-CH), 128.7 (Ar*C*H), 130.9 (Ar*C*H), 136.0 (Ar*C*), 138.7 (Ar*C*), 156.0 (O*C*C=O), 159.2 (Ar*C ipso*-oxygen); MS (ES+): *m*/*z* = 260.77 [M + Na]$^+$.

For full experimental details, spectroscopic and analytical data, along with a discussion on the assignment of the configurations, see the Supporting Information.