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# Stereoselective synthesis of 3,4-disubstituted tetrahydrofurans and 2,3,4-trisubstituted tetrahydrofurans using an intramolecular allylation strategy employing allylsilanes

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**Abstract**

A Brønsted acid-mediated intramolecular allylation involving an allylsilane and an aldehyde has been used as the key step in a stereoselective synthesis of 3,4-disubstituted tetrahydrofurans and 2,3,4-trisubstituted tetrahydrofurans.


*Keywords:* Allylsilanes; Tetrahydrofurans; Cyclisation; Intramolecular allylation; Brønsted acids

Substituted tetrahydrofurans are attractive synthetic targets owing to their frequent occurrence in natural products.[1] Of the range of substitution patterns that are available, the 2,3,4-trisubstitution pattern is found in a number of natural products; some examples are shown in Figure 1. Pachastrissamine (jaspine B) exhibits anti-cancer activity,[2,3] whilst (+)-gynunone, which contains the core motif within a tricyclic framework, displays anti platelet aggregation activity.[4] Aureonitol is a fungal metabolite of unknown biological activity.[5] As part of a research programme investigating the use of silyl nucleophiles in cyclisation strategies,[6] we now wish to describe an intramolecular allylation approach to this class of substituted oxygen heterocycle.[7]

We recently reported an intramolecular allylation route to 2,4,5-trisubstituted tetrahydropyrans.[6c] In this work, Brønsted acid activation of aldehyde **1** effected cyclisation to afford the corresponding 2,4,5-trisubstituted tetrahydropyran in excellent yield and diastereoselectivity, with only two out of the four possible tetrahydropyran products, **2** and **3**, ever being observed. Assuming cyclisation proceeds through a chair-like transition state in which the substituent at the carbinol stereogenic centre adopts a pseudoequatorial orientation, the observed complete 1,4-stereoinduction can be explained by the allylsilane adopting a pseudoequatorial orientation thereby minimising steric interactions. Excellent 1,3-stereoinduction (up to 50:1), favouring the pyran product **2** in which the hydroxyl substituent occupies an axial orientation, is also achievable by carrying out the reaction in an apolar solvent. This stereoselectivity can be explained on electrostatic grounds using a modified Evans dipole model (Scheme 1).[8]

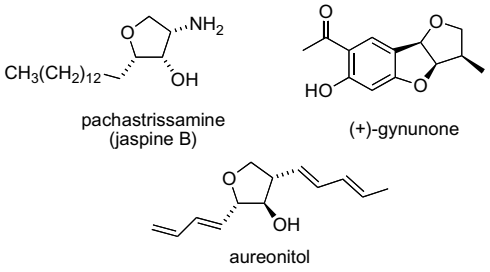


Fig. 1. 2,3,4-Trisubstituted tetrahydrofurans occur in a range of natural products.

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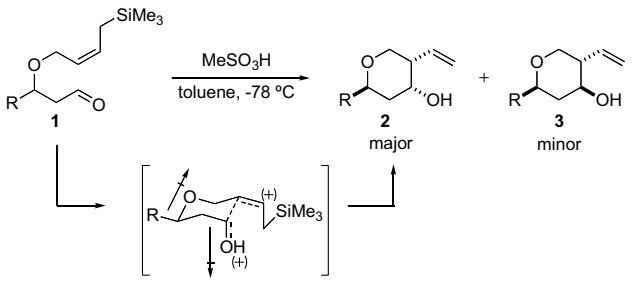
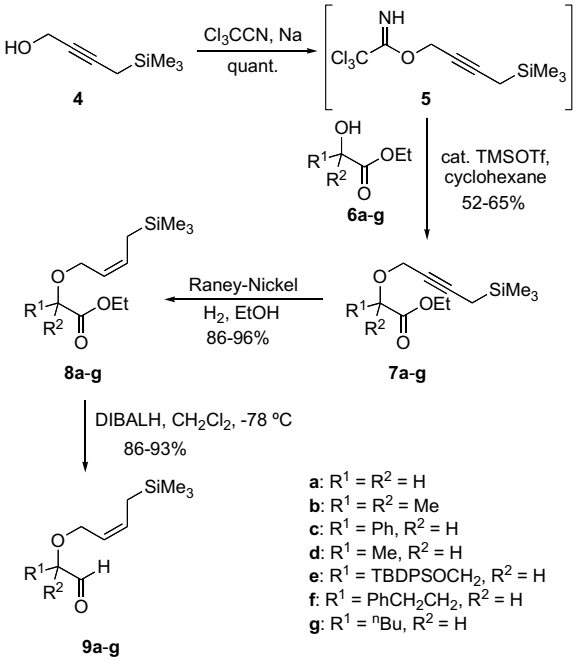



Scheme 1. Stereoselective synthesis of 2,4,5-trisubstituted tetrahydropyrans.

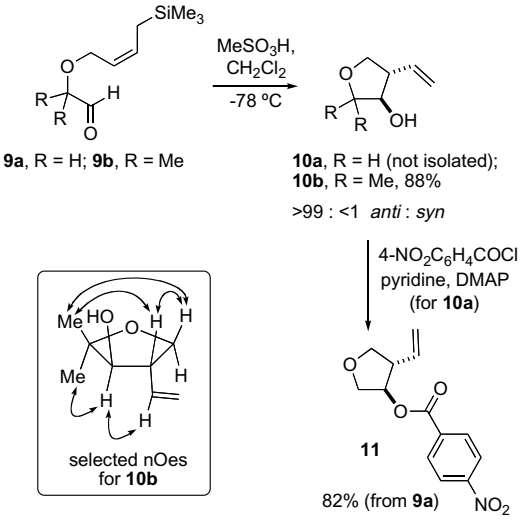
Removing the methylene unit between the aldehyde and carbinol stereogenic centre in **1** would provide a system **9** that is set up to afford the corresponding 2,3,4-trisubstituted tetrahydrofuran on activation. Synthesis of this cyclisation precursor began with etherification of α-hydroxy ester **6** (Scheme 2). In order to avoid epimerisation of the stereogenic centre (vide infra) in this alcohol starting material, we elected to introduce the propargylsilane using a non-basic etherification procedure.[9] To this end, trichloroacetimidate **5** was synthesised as described previously from propargyl alcohol **4**.[6c] Acetimidate **5** was then used directly, without purification, in a TMSOTf-mediated etherification with α-hydroxy ester **6**,[10] to afford ether **7** in good yield. The next step required the partial hydrogenation of the triple bond in **7**. This was best achieved using Raney-nickel under a hydrogen atmosphere,[11] which generated the desired (*Z*)-allylsilane **8** with excellent selectivity. Even under these optimised conditions, however, trace amounts of the over-reduction product were still observed for all substrates except for **8b**, where approximately 10% over-reduction was obtained.[12] Having installed the allylsilane nucleophile, DIBALH reduction of the ester group in **8** proceeded uneventfully to release the aldehyde electrophile and our cyclisation precursor **9** (Scheme 2).




Scheme 2. Synthesis of cyclisation precursors.

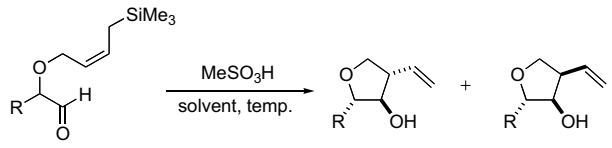
We commenced our intramolecular allylation study with substrate **9a**, which lacks a stereogenic centre at the 2-position. Using this substrate would allow us to examine the relative stereochemistry of the two new stereogenic centres, which are generated in the cyclisation product, without the complicating issue of existing stereochemistry in the starting material. Employing the conditions, which had proven so successful in our previous work,[6c] aldehyde **9a** was treated with $MeSO_3H$ in $CH_2Cl_2$ at −78 °C. To avoid potential problems associated with isolating the volatile product, the resulting tetrahydrofuran **10a** was trapped in situ with 4-nitrobenzoyl chloride to generate the corresponding 4-nitrobenzoate ester **11** as a single diastereoisomer. Achiral aldehyde **9b**, containing a quaternary centre at the 2-position also cyclised smoothly to provide tetrahydrofuran **10b**, once again as a single diastereoisomer (Scheme 3). The relative stereochemistry in these two products was readily determined by NOE experiments (figure inset, Scheme 3).

We next switched our attention to aldehyde **9c**, which contains a stereogenic centre α to the carbonyl group. Cyclisation of this class of substrate could generate up to four diastereoisomeric products. In the event however, aldehyde **9c** reacted under our favoured conditions ($MeSO_3H$, $CH_2Cl_2$, −78 °C) with complete 1,2-stereoinduction (vide infra), to afford two out of the possible four diastereoisomers **10c** and **12c** (Table 1, entry 1). In a bid to improve the more modest 1,3-stereoinduction (5.5:1), a variety of different solvents were screened over a range of temperatures (Table 1, entries 1–7). In all cases, the same two allylation products were observed on analysis of the crude reaction mixture by $^1H$ NMR spectroscopy; however




Scheme 3. Intramolecular allylation was completely stereoselective in the absence of existing stereochemical information.

Table 1
Optimisation of the intramolecular allylation and investigation of reaction scope




| Entry | *R* | Solvent | Temp (°C) | Ratio **10**:**12** | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | Ph | $CH_2Cl_2$ | −78 | 5.5:1.0 | 90 |
| 2 | Ph | PhMe | −78 | 4.0:1.0 | 81 |
| 3 | Ph | THF | −78 | 3.5:1.0 | 62 |
| 4 | Ph | $Et_2O$ | −78 | 4.0:1.0 | 68 |
| 5 | Ph | MeCN | −40 | 3.5:1.0 | 78 |
| 6 | Ph | acetone | −78 | 4.0:1.0 | 81 |
| 7 | Ph | $CHCl_3$ | −50 | 7.0:1.0 | 88 |
| 8 | Me | $CHCl_3$ | −50 | 5.0:1.0 | 91 |
| 9 | $TBDPSOCH_2$ | $CHCl_3$ | −50 | 8.0:1.0 | 86 |
| 10 | $PhCH_2CH_2$ | $CHCl_3$ | −50 | 10.0:1.0 | 85 |
| 11 | $^n$Bu | $CHCl_3$ | −50 | 7.0:1.0 | 89 |

[a] Isolated yield of **10** and **12** combined.

disappointingly, significant improvements in 1,3-stereoinduction were not observed, with the use of chloroform as the solvent at −50 °C providing the best result (7:1) (Table 1, entry 7).[13] These optimised conditions were then extended to a range of aldehydes **9d–g** (Table 1, entries 8–11). In all cases, reaction was rapid (<10 min) and the tetrahydrofuran products were isolated in excellent yield. Moreover, the cyclisation again proceeded with complete 1,2-stereoinduction for all substrates, with the levels of 1,3-stereoinduction being more modest, ranging from 5:1 in the worst case (Table 1, entry 8) up to 10:1 for the best (Table 1, entry 10). The two diastereoisomeric tetrahydrofuran products **10** and **12** were generally isolated and characterised as a mixture apart from the phenyl and phenethyl derivatives, which were readily separable by flash column chromatography.

The $^1$H NMR spectra for the major diastereoisomers **10c–g** displayed similar patterns (appearance of the resonances for the protons around the common tetrahydrofuran unit), which suggested the same relative stereochemistry was present in all cases. Assignment of the relative stereochemistry in this diastereoisomer was provisionally made on the basis of NOE experiments (Fig. 2). Further proof was obtained by oxidising phenyl derivative **10c** to the corresponding ketone **13** with Dess Martin periodinane (Scheme 4). Subsequent reduction of **13** with the bulky reducing agent, L-Selectride, afforded the epimeric tetrahydrofuran **14** with high stereoselectivity.[14] Such high stereoselectivity in this reduction is consistent with a 1,3-*syn* relationship in the starting ketone, which ensures the diastereotopic faces of the carbonyl group are strongly differentiated on steric grounds by the two α-substituents. The structure of **14** was elucidated by X-ray crystallography (Fig. 2),[15] which confirmed that reduction of ketone **13** had indeed occurred by hydride attack on the less hindered

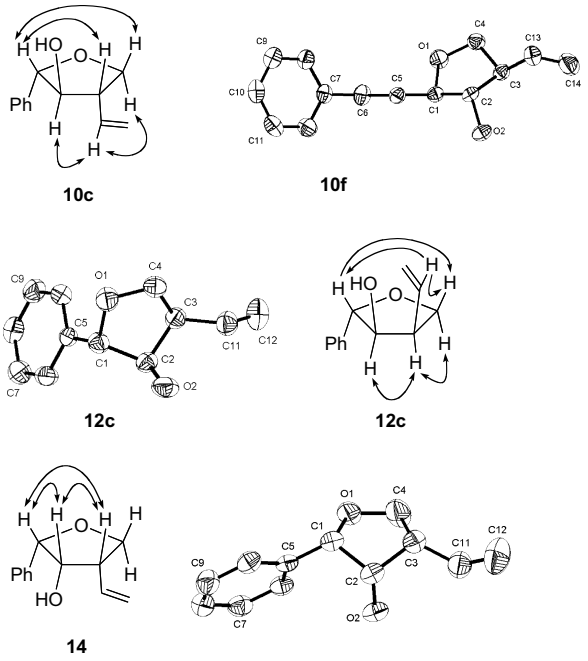
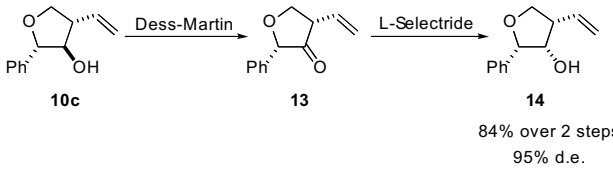



Fig. 2. Selected NOE data for **10c** (top), **12c** (middle) and **14** (bottom) and ORTEP plots for **10f** (top), **12c** (middle) and **14** (bottom). Atomic displacement parameters at 293 K are drawn at the 30% probability level.




Scheme 4. An oxidation–reduction sequence on the major diastereoisomer **10c** provided epimeric tetrahydrofuran **14**.

diastereoface.[16] This set of experiments provided an indirect elucidation of the major diastereoisomer; however final proof was obtained by X-ray analysis of the phenethyl derivative **10f** (Fig. 2).[15] Having identified the two diastereoisomeric tetrahydrofurans possessing a 1,3-*syn* relationship, the minor diastereoisomer **12** had to contain a 1,3-*anti* relationship by default. This was confirmed by NOE experiments which also identified a 1,2-*anti*-2,3-*syn* stereochemical relationship in this product. Final proof of structure was again obtained by X-ray analysis of the phenyl derivative **12c** (Fig. 2).[15]

Although we had been careful to employ a non-basic etherification procedure to form our ether linkage in aldehyde **9c**, we were still keen to check that possible erosion of stereochemical information in our starting material had not occurred at any point along our synthetic route. To this end, tetrahydrofuran **10c**, which was accessed from racemic ethyl mandelate, was analysed by chiral HPLC and baseline separation of the two enantiomers was readily achieved (Fig. 3a). Repeating the synthesis, but this time starting from (*S*)-ethyl mandelate, we were pleased to observe that

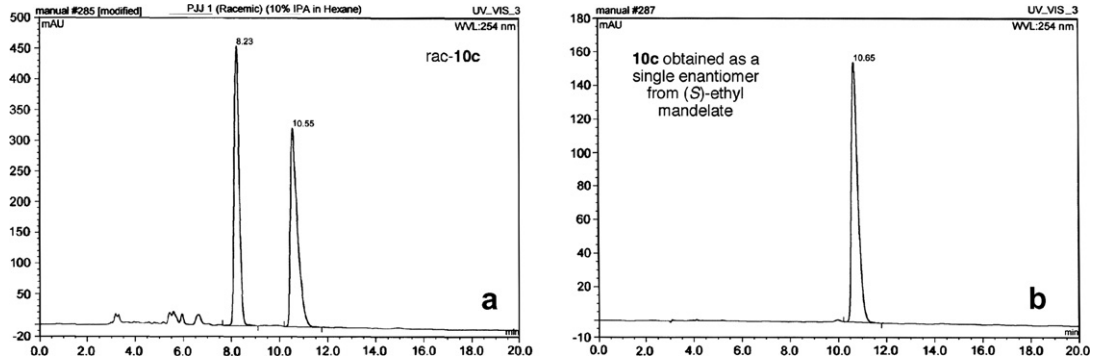



Fig. 3. HPLC data showing erosion of stereochemical information is not observed in the synthetic sequence.

the major diastereoisomer **10c** was of a single configuration when analysed by chiral HPLC (Fig. 3b). This result conclusively demonstrates that no erosion of stereochemistry had occurred at any point along the synthetic route.

Attaching the allylsilane to the aldehyde through a relatively short tether of just three atoms limits the number of possible approach trajectories for the nucleophile on the electrophile. To rationalise the stereochemical outcome of the cyclisation reaction involving aldehydes **9**, we propose the two transition states shown in Figure 4. In both cases, the *R* substituent occupies a pseudoequatorial orientation on steric grounds. The complete 1,2-stereoinduction can then be understood by the aldehyde adopting a pseudoequatorial position, which orients the dipole moments across the polar C–O and C=O bonds in opposite directions.[17] Rationalising the observed 1,3-stereoinduction is more difficult although we tentatively propose that the transition state (T.S.1) in which the allylsilane adopts a pseudoaxial orientation is favoured by minimising eclipsing steric interactions between the carbonyl electrophile and approaching nucleophile.

In summary, we have developed a stereoselective route to 3,4-disubstituted tetrahydrofurans and 2,3,4-trisubstituted tetrahydrofurans. Ring formation is achieved through Brønsted acid-mediated allylation of an allylsilane and an aldehyde. When stereochemical information is absent from the cyclisation precursor, the reaction is highly diastereoselective for a single product. The problem is more complex when a stereogenic centre is introduced into the substrate. In these cases, cyclisation provides two of the four possible tetrahydrofurans. Transition states have been proposed to rationalise the stereoselectivity of these reactions. Future work will now focus on the application of this methodology to the synthesis of biologically important natural products.

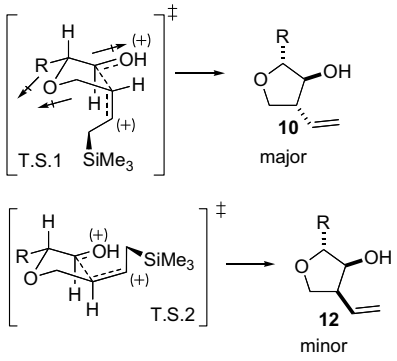



Fig. 4. Transition states leading to the two allylation products.

## Acknowledgements

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10. We have found the use of 0.1 equiv of TMSOTf to be more effective than our previously described approach (see Ref. 6c) using stoichiometric TMSOTf in the presence of a Brønsted acid scavenger.
11. Use of Lindlar catalyst led to appreciable amounts of over-reduction.
12. The over-reduction product was not separated from the desired allylsilane but was readily separable from the tetrahydrofuran cyclisation products.
13. *Representative experimental procedure*: $MeSO_3H$ (42 μL, 0.63 mmol) was added to a solution of aldehyde **9c** (150 mg, 0.57 mmol, prepared from (*S*)-ethyl mandelate) in $CHCl_3$ (6 mL) at −50 °C. After 5 min, satd $NaHCO_3$ solution (6 mL) was added and the reaction mixture was allowed to warm to rt over 30 min. The two phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 6 mL). The combined organic fractions were washed with $H_2O$ (6 mL), and brine (6 mL) and then dried ($MgSO_4$). Filtration and evaporation of the solvent under reduced pressure provided a mixture of tetrahydrofurans (7:1 **10c**:**12c**) which were separated by flash column chromatography (6% EtOAc in $CH_2Cl_2$) to provide, in order of elution, alcohol **10c** as a viscous, colourless oil (83 mg, 77%); $R_f = 0.24$ (6% EtOAc in $CH_2Cl_2$); $[\alpha]_D^{23}$ −29.9 (*c* 1.00, $CHCl_3$); (found: C, 75.41; H, 7.12%. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%); $\nu_{max}$(film)/cm$^{-1}$ 3401 br s (OH), 1643 m (C=C); $\delta_H$ (300 MHz) 1.87 (1H, br s, O*H*), 2.97 (1H, app. quintet, *J* 8.1, 4-*H*), 3.88 (1H, app. t, *J* 5.9, 3-*H*), 3.93 (1H, app. t, *J* 8.8, 5-$H_a$), 4.26 (1H, app. t, *J* 7.3, 5-$H_b$), 4.64 (1H, d, *J* 7.4, 2-*H*), 5.13 (1H, d with unresolved fine coupling, *J* 10.3, CH=C$H_{cis}H_{trans}$), 5.21 (1H, d with unresolved fine coupling, *J* 17.3, C*H*=C$H_{cis}H_{trans}$), 5.67–5.82 (1H, m, C*H*=$CH_2$), 7.21–7.43 (5H, m, Ph*H*); $\delta_C$ (125 MHz) 52.4 (CH, *C*-4), 71.1 ($CH_2$, *C*-5), 83.2 (CH, *C*-3), 85.6 (CH, *C*-2), 117.6 ($CH_2$, *C*H=$CH_2$), 125.8 (CH, Ph), 127.8 (CH, Ph), 128.5 (CH, Ph), 136.2 (CH, *C*H=$CH_2$), 140.3 (quat. C, *ipso*Ph); *m*/*z* (EI) 190 ([M]$^+$, 0.5%), 161 (4), 136 (5), 119 (6), 107 (100), 91 (13), 79 (15), 55 (8); and then alcohol **12c** as a white solid (12 mg, 11%); mp 64–65 °C; $R_f = 0.22$ (6% EtOAc in $CH_2Cl_2$); $[\alpha]_D^{23}$ +3.2 (*c* 1.00, $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$ 3416 br s (OH), 1643 m (C=C); $\delta_H$ (300 MHz) 2.12 (1H, br s, O*H*), 2.87–3.12 (1H, m, 4-*H*), 4.00 (1H, app. t, *J* 9.0, 5-$H_a$), 4.15 (1H, dd, *J* 5.1, 2.6, 3-*H*), 4.27 (1H, app. t, *J* 8.1, 5-$H_b$), 4.96 (1H, d, *J* 2.6, 2-*H*), 5.20 (1H, d with unresolved fine coupling, *J* 17.3, CH=C$H_{cis}H_{trans}$), 5.28 (1H, d with unresolved fine coupling, *J* 10.3, CH=C$H_{cis}H_{trans}$), 5.83–5.98 (1H, m, C*H*=$CH_2$), 7.21–7.32 (5H, m, PhH); $\delta_C$ (125 MHz) 47.0 (CH, *C*-4), 70.8 ($CH_2$, *C*-5), 80.4 (CH, *C*-2), 87.6 (CH, *C*-3), 119.4 ($CH_2$, *C*H=$CH_2$), 125.3 (CH, Ph), 127.4 (CH, Ph), 128.4 (CH, Ph), 132.7 (CH, CH=$CH_2$), 140.9 (quat. C, *ipso*Ph); *m*/*z* (EI) 191 ([M+H]$^+$, 0.5%), 173 (83, [M−OH]$^+$), 151 (100), 121 (25), 106 (89), 92 (14), 84 (45), 77 (15), 56 (24), 44 (5).
14. *Data for* **14** (*prepared from (S)-ethyl mandelate*): $R_f = 0.28$ (6% EtOAc in $CH_2Cl_2$); $[\alpha]_D^{23}$ −8.7 (*c* 1.00, $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$ 3406 br s (OH), 1645 w (C=C); $\delta_H$ (300 MHz) 1.25 (1H, br s, OH), 3.08–3.21 (1H, m, 4-*H*), 4.06 (1H, dd, *J* 10.7, 8.1, 5-$H_a$), 4.15 (1H, app. t, *J* 8.1, 5-$H_b$), 4.23 (1H, app. t, *J* 3.0, 3-*H*), 5.10 (1H, d, *J* 3.0, 2-*H*), 5.16 (1H, d, *J* 11.4, CH=C$H_{cis}H_{trans}$), 5.21 (1H, d, *J* 16.9, CH=C$H_{cis}$-$H_{trans}$), 5.91–6.06 (1H, m, C*H*=$CH_2$), 7.25–7.42 (5H, m, Ph*H*); $\delta_C$ (75 MHz) 49.8 (CH, *C*-4), 70.9 ($CH_2$, *C*-5), 75.8 (CH, *C*-3), 85.6 (CH, *C*-2), 118.1 ($CH_2$, CH=*C*$H_2$), 126.7 (CH, Ph), 127.9 (CH, Ph), 128.5 (CH, Ph), 133.5 (CH, *C*H=$CH_2$), 137.0 (quat. C, *ipso*Ph); *m*/*z* (EI) 190 ($M^+$, 1%), 161 (4), 136 (7), 119 (12), 115 (5), 107 (100), 91 (42), 91 (44), 79 (53), 55 (47), 51 (14); HRMS *m*/*z* (EI) 190.1002. $C_{12}H_{14}O_2$ requires 190.9940.
15. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. **10f** CCDC 677099; **12c** CCDC 677098; **14** CCDC 677100. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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