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Synthesis of 1,3-Dihydrobenzo[*c*]furans from Ortho-Lithiated Aryloxiranes

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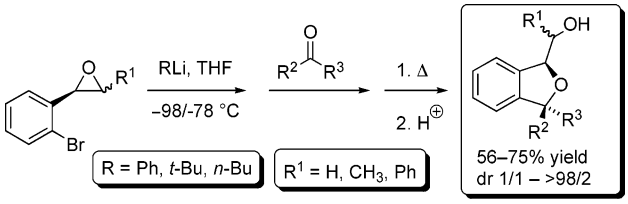


A general method for the synthesis of hydroxyalkyl 1,3-dihydrobenzo[*c*]furans from ortho-lithiated aryloxiranes and carbonyl compounds is described.

The 1,3-dihydrobenzo[*c*]furan derivatives (phthalans) represent an important class of oxygenated heterocycles because of their interesting biological properties. In particular, 1,3-dihydrobenzo[*c*]furans may show antidepressive, antifungal, antisecretory, and antihistaminic activities.[1]

One of the most employed methodologies for the direct synthesis of 1-substituted as well as 1,3-disubstituted 1,3-dihydrobenzo[*c*]furans involves the benzylic deprotonation−alkylation sequence of the preformed isobenzofuran ring.[2] The use of ortho-metalated intermediates had been used by Parham, Maddaluno, and Knochel for the construction of the phthalan skeleton.[3] Few other methods have been used toward the same goal.[4]

In the course of our studies on the utility of ortho-lithiated aryloxiranes and arylaziridines as intermediates in the construction of bicyclic molecules,[5] we reasoned that addition of ortho-lithiated aryloxiranes to carbonyl compounds might be employed for the preparation of 1,3-dihydrobenzo[*c*]furans following a domino process involving a hydroxyalkylation of the phenyl ring and subsequent nucleophilic epoxide ring-opening in a 5-exo mode (Scheme 1).[6]

SCHEME 1. Retrosynthetic Approach to 1,3-Dihydrobenzo[*c*]furans

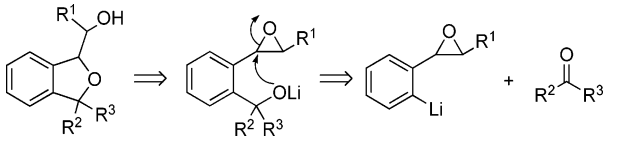
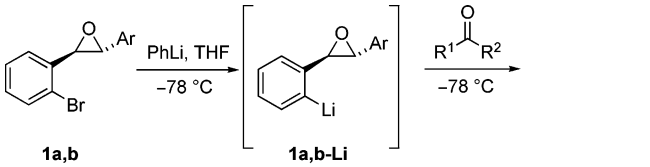
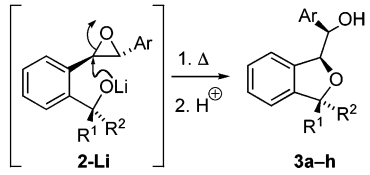


TABLE 1. Synthesis of 1,3-Dihydrobenzo[*c*]furans 3a−h from *o*-Bromo-*trans*-stilbene Oxides 1a,b and Carbonyl Compounds





entry	oxirane	Ar	R^1	R^2	phthalan **3** (yield, %)[a]	dr[b]
1	**1a**	Ph	Me	Me	**3a** (64)	>98/2
2	**1a**	Ph	$-(CH_2)_5-$		**3b** (67)	>98/2
3	**1b**	*p*-Tolyl	Me	Me	**3c** (69)	>98/2
4	**1a**	Ph	H	Ph	**3d** (−)[c]	
5	**1a**	Ph	H	*t*-Bu	**3e** (65)	50/50[d]
6	**1a**	Ph	Ph	*n*-Pr	**3f** (75)	67/33[e]
7	**1b**	*p*-Tolyl	H	CH═CHPh	**3g** (68)	50/50[e]
8	**1b**	*p*-Tolyl	Ph	CH═CHPh	**3h** (65)	50/50[e]

[a] Isolated yields after column chromatography on silica gel. [b] Diastereomeric ratio calculated by ^{1}H NMR analysis on the crude reaction mixture. [c] In this case, the hydroxyalkylated stilbene oxide **2d** was the only product isolated (72% yield, dr 67/33). [d] Inseparable mixture of diastereoisomers. [e] Separable mixture of diastereoisomers (petroleum ether/AcOEt 7−8/3−2, see the Supporting Information).

Under optimized reaction conditions (PhLi, −78 °C, 45 min)[5a] for the lithium−bromine exchange of the *o*-bromo-*trans*-stilbene oxide **1a**, we generated the organolithium **1a-Li** (Table 1, entry 1), which reacted with acetone and cyclohexanone to give the ortho-substituted intermediates **2a-Li** and **2b-Li** that spontaneously cyclized to give, after acidic quenching, the 1,3-dihydrobenzo[*c*]furans **3a** (64%) and **3b** (67%) as sole diastereoisomers, respectively (Table 1, entries 1 and 2). In a similar way, in the coupling reaction of *o*-lithiostilbene oxide **1b-Li**, generated from **1b**, with acetone we obtained the 1,3-dihydrobenzo[*c*]furan **3c** in a 69% yield (Table 1, entry 3).

1,3-Dihydrobenzo[*c*]furans variously substituted in position 3 were synthesized varying the carbonyl compound (Table 1).

(1) (a) Lovey, R. G.; Elliott, A. J.; Kaminski, J. J.; Loebenberg, D.; Parmegiani, R. M.; Rane, D. F.; Girijavallabham, V. M.; Pike, R. E.; Guzik, H.; et al. *J. Med. Chem.* **1992**, *35*, 4221−4229. (b) Ram, S.; Saxena, A. K.; Jain, P. C.; Patnaik, G. K. *Indian J. Chem. Sect. B* **1984**, *23*, 1261. (c) Klohs, M. W.; Petracek, F. J. (Dart Industries Inc.), US Patent 3471519, **1969**, *71*, 124212.

(2) (a) Sarkar, T. K.; Basak, S. *Org. Lett.* **2004**, *6*, 2925−2927. (b) Fort, Y.; Gros, P.; Rodriguez, A. L. *Tetrahedron Lett.* **2002**, *43*, 4045−4048. (c) Zemolka, S.; Lex, J.; Schmalz, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2525−2528. (d) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667−2722. (e) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *J. Organomet. Chem.* **1989**, *379*, 81−88.

(3) (a) Parham, W. E.; Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 4804−4806. (b) Martin, C.; Mailliet, P.; Maddaluno, J. *J. Org. Chem.* **2001**, *66*, 3797−3805. (c) Delacroix, T.; Bérillon, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 8108−8110.

(4) (a) Ewing, D. F.; Len, C.; Mackenzie, G.; Ronco, G.; Villa, P. *Tetrahedron: Asymmetry* **2000**, *11*, 4995−5002. (b) Tsukada, N.; Sugawara, S.; Nakaoka, K.; Inoue, Y. *J. Org. Chem.* **2003**, *68*, 5961−5966.

(5) (a) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Salomone, A.; Gasparrini, F. *Org. Lett.* **2005**, *7*, 4895−4898. (b) Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005**, *7*, 3749−3752.

(6) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−738.

10.1021/jo052645t CCC: $33.50
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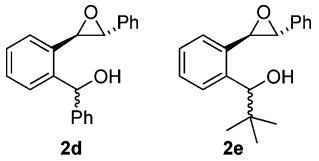
CHART 1



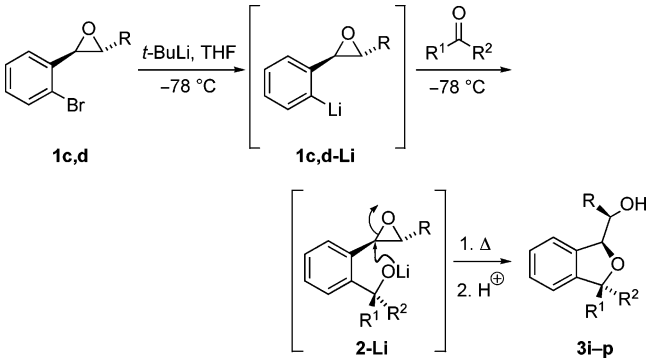
The reaction of **1a-Li** with aldehydes (Table 1, entries 4 and 5) resulted in the formation of the hydroxyalkylated stilbene oxides **2d** and **2e** that could be easily isolated (Chart 1). The "Thorpe−Ingold effect"[7] and the steric hindrance might explain the sluggishness of **2d** and **2e** to cyclize to the corresponding dihydrobenzo[*c*]furans. The epoxide **2e** could be converted into a chromatographically separable diastereomeric mixture of 1,3-dihydrobenzo[*c*]furans **3e** by warming the reaction mixture to room temperature and stirring overnight, whereas the epoxide **2d** did not cyclize even after 12 h at room temperature.

Unfortunately, the reaction with either unsymmetrical or α,*β*-unsaturated carbonyl compounds proceeded with poor diastereoselectivity at the new stereogenic center giving a mixture of stereoisomeric 1,3-dihydrobenzo[*c*]furans, which, however, could be separated by column cromatography on silica gel (Table 1, entries 6−8); in particular, in the case of *trans*-cinnamaldehyde and *trans*-chalcone, a regioselective 1,2-addition of **1b-Li** took place giving the 3-alkenyl-1,3-dihydrobenzo[*c*]furans **3g,h**.

To demonstrate the general applicability of this methodology, the reactions of *o*-bromostyrene oxide **1c**, *trans*-phenylpropylene oxide **1d,** and *cis*-stilbene oxide **1e** have been investigated. The lithium−bromine exchange of the epoxides **1c**,**d** proceeded in low yield by using PhLi; we found that 2 equiv of *t*-BuLi at −78 °C for 15 min were the best conditions for lithiation. The resulting organolithiums **1c-Li** and **1d-Li** reacted with acetone in a stereospecific manner to furnish 1,3-dihydrobenzo[*c*]furans **3i,j** in a 56% and 67% yield, respectively (Table 2, entries 1,2); in contrast, the reaction of both **1c-Li** and **1d-Li** with benzaldehyde, pivalaldehyde, and butyrophenone furnished 1,3-dihydrobenzo[*c*]furans **3k**−**p** (Table 2, entries 3−8) as an almost 1:1 diastereomeric mixture with the exception of **3n**,**o** which formed in appreciable diastereoselectivity (dr = 77/23). *o*-Bromo-*cis*-stilbene oxide **1e**, instead, underwent clean bromine−lithium exchange only when *n*-BuLi (1 equiv) was used at −98 °C for 45 min. The addition of acetone to the resulting *o*-lithio derivative **1e-Li** led the diastereospecific formation (dr > 98:2) of 1,3-dihydrobenzo[*c*]furan **3q**, whereas the reaction with pivalaldehyde gave a 1:1 diastereomeric mixture of 1,3-dihydrobenzo[*c*]furans **3r** after cyclization of the hydroxyalkyloxirane intermediate **2r** (Scheme 2, see also the Experimental Section).

The relative configuration of the two stereocenters (1*R**,1′*S**) of compounds **3a**−**c**,**j** (see Tables 1 and 2) was established considering that there is inversion of configuration at the benzylic carbon attacked by the lithium alkoxide and retention at the other carbon of the starting epoxide; this assignment was confirmed by the X-ray analysis in the case of **3a**.[8] The stereochemistry of compounds **3f**−**h** and **3k**,**l** was, instead, established detecting positive NOE effects, diagnostic of a spatially close hydrogens relationship, after applying selective ^{1}H preirradiations within a double pulsed field gradient spin−echo NOE (DPFGSE-NOE) sequence.[9] Indeed, as shown in Chart 2, in the case of 1,3-dihydrobenzo[*c*]furans **3f** and **3g**,**h**, for a certain isomer, a preirradiation of H_A enhanced either the nearest propyl methylenic protons of **3f** or the vinylic protons of **3g**,**h**, whereas, for the other isomer, similar enhancements were produced only upon irradiation of H_B. In the case of diasteromeric 1,3-dihydrobenzo[*c*]furans **3k**,**l**, NOE enhancement of H_C was gained upon selective preirradiation of H_A, or of H_B, thus demonstrating their relative stereochemistry.

TABLE 2. Synthesis of 1,3-Dihydrobenzo[*c*]furans 3i−p from *o*-Bromostyrene Oxides 1c,d and Carbonyl Compounds



entry	oxirane	R	R^1	R^2	phthalan **3** (yield, %)[a]	dr[b]
1	**1c**	H	Me	Me	**3i** (56)	
2	**1d**	Me	Me	Me	**3j** (67)	>98/2
3	**1c**	H	H	Ph	**3k** (70)	58/42[c]
4	**1d**	Me	H	Ph	**3l** (73)	50/50[c]
5	**1c**	H	H	*t*-Bu	**3m** (60)	50/50[d]
6	**1d**	Me	H	*t*-Bu	**3n** (65)	77/23[d]
7	**1c**	H	Ph	*n*-Pr	**3o** (60)	77/23[d]
8	**1d**	Me	Ph	*n*-Pr	**3p** (65)	55/45[d]

[a] Isolated yields after column chromatography on silica gel. [b] Diastereomeric ratio calculated by ^{1}H NMR analysis on the crude reaction mixture. [c] Separable mixture of diastereoisomers (petroleum ether/AcOEt 7−8/3−2, see the Supporting Information). [d] Inseparable mixture of diastereoisomers.

The present synthetic strategy could be successfully extended to the preparation of optically pure 1-hydroxyalkyl-1,3-dihydrobenzo[*c*]furans. Treatment of (*S*,*S*)-**1a**[5a] with PhLi generated (*S*,*S*)-**1a-Li**. The addition of acetone resulted in the formation of the optically pure 1,3-dihydrobenzo[*c*]furan (+)-**3a** (60% yield). The ee value of (+)-**3a** (ee >95%) was determined by ^{1}H NMR in the presence of a chiral cosolvating agent (Scheme 3, see also the Supporting Information).[10]

In conclusion, we have developed a simple strategy for the synthesis of hydroxyalkyl-1,3-dihydrobenzo[*c*]furans based on the reaction of cis and trans configurated ortho-lithiated aryloxiranes with carbonyl compounds. The methodology can also be applied to the stereospecific synthesis of highly enantiomerically enriched 1,3-dihydrobenzo[*c*]furan derivatives starting from chiral nonracemic stilbene oxides.

Experimental Section

Preparation of 1,3-Dihydrobenzo[*c*]furans 3a−p. General Procedure. A solution of PhLi (1.0 mmol, 0.5 mL of a 1.8 M

(7) (a) Beesley, R M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080−1106. (b) Ingold, C. K. *Ibid.* **1921**, *119*, 305−329.

(8) Crystallographic data for compound **3a** have been deposited at the Cambridge Crystallographic Data Centre (deposition no. CCDC-293337). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: (int.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

(9) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989; p 264.

(10) Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1457.

SCHEME 2. Synthesis of 1,3-Dihydrobenzo[*c*]furans 3q,r

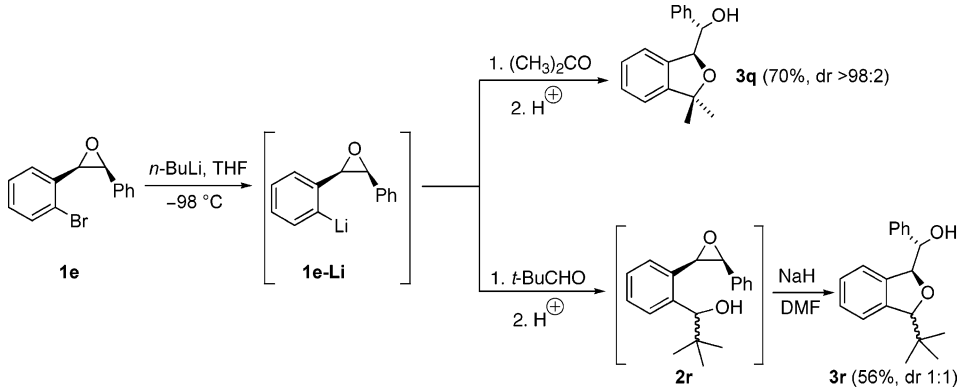
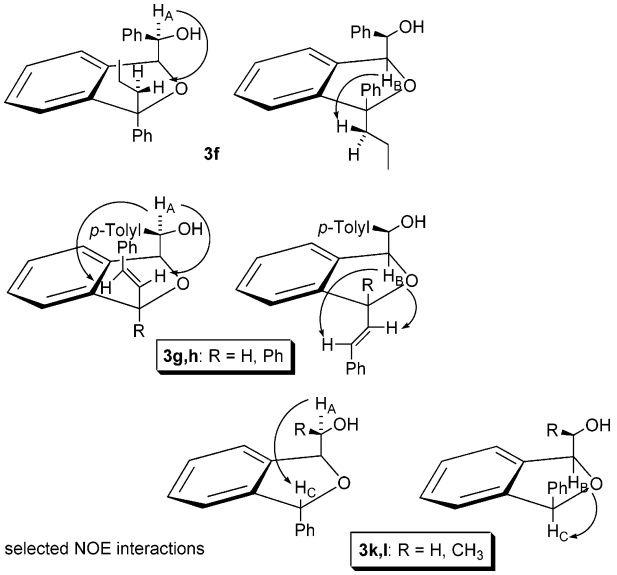
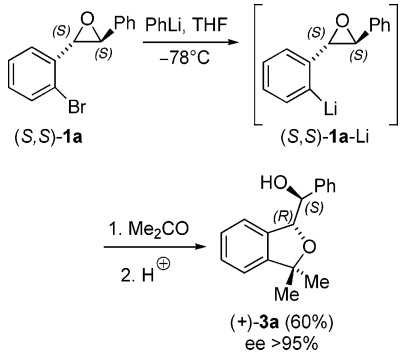


CHART 2



SCHEME 3. Synthesis of Optically Active 1,3-Dihydrobenzo[c]furan (+)-3a



solution in *n*-dibutyl ether) [or *t*-BuLi (2.0 mmol, 1.2 mL of a 1.7 M solution in pentane) in the cases of oxiranes **1c**,**d**] was added to a precooled (−78 °C, dry ice/acetone bath) solution of oxiranes **1a**,**b** (1.0 mmol) in THF (6 mL) under N_2 and stirring. After 45 min (or 15 min in the case of oxiranes **1c**,**d**) at this temperature, a solution of the carbonyl compound (1.5 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for 20 min at −78 °C; after this time, it was allowed to warm to rt (and stirred for an additional 12 h in the case of hydroxyalkyloxirane **2e**), quenched with satd aq NH_4Cl, and extracted with Et_2O (3 × 20 mL). The solvent was removed under reduced pressure and the crude residue purified by flash column chromatography (silica gel; petroleum ether/AcOEt 7−8/3−2) to give compounds **3a**−**p**.

(1*R,1′*S**)-(3,3-Dimethyl-1,3-dihydrobenzo[*c*]furan-1-yl)phenylmethanol (3a):** white solid; mp 77−78 °C (hexane); 64%, dr > 98/2; ^{1}H NMR (500 MHz) δ 1.45 (s, 3 H), 1.50 (s, 3 H), 2.58 (br s, exchanges with D_2O, 1 H), 5.07 (d, J = 4.0 Hz, 1 H), 5.49 (d, J = 4.0 Hz, 1 H), 6.58 (d, J = 7.8 Hz, 1 H), 7.06−7.12 (m, 2 H), 7.23−7.40 (m, 6 H); ^{13}C NMR (125 MHz) δ 29.2, 29.5, 75.1, 85.4, 85.5, 120.4, 122.9, 124.3, 126.5, 126.9, 127.5, 128.1, 136.5, 139.5, 147.9; GC−MS (70 eV) *m*/*z* 237 (M^+ − OH, 3), 147 (100), 129 (37), 105 (8), 77 (14); FT-IR (film, cm^{-1}) 3418, 3030, 2971, 2924, 1454, 1361, 1027, 759, 701. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.33; H, 6.95. **(1*R*,1′*S*)-3a:** 60%; $[\alpha]^{20}_D$ = +20 (*c* 0.5, $CHCl_3$).

Preparation of 1,3-Dihydrobenzo[*c*]furans 3q,r. General Procedure. A solution of *n*-BuLi (1.0 mmol, 0.4 mL of a 2.5 M solution in hexanes) was added to a precooled (−98 °C, methanol−liquid nitrogen bath) solution of oxirane **1e** (1.0 mmol) in THF (6 mL) under N_2 and stirring. After 45 min at this temperature, a solution of the carbonyl compound [$(CH_3)_2CO$ or *t*-BuCHO, 1.5 mmol] in THF (2 mL) was added dropwise. The resulting mixture was stirred for 20 min at −78 °C; after this time, it was allowed to warm to rt, quenched with satd aq NH_4Cl, and extracted with Et_2O (3 × 20 mL). The solvent was then removed under reduced pressure. In the case of the reaction with acetone, the phthalan **3q** was straightforwardly obtained and was purified by flash column chromatography (silica gel; petroleum ether/AcOEt 8/2). On the other hand, the crude hydroxyalkyloxirane **2r**, formed in the reaction with pivalaldehyde, was then dissolved in dry DMF (141 mg, 0.5 mmol in 2 mL) and treated with NaH (60% oil dispersion, 38 mg, 1 mmol) under N_2 at rt; the resulting mixture was stirred for 12 h. After this time, the reaction was quenched with satd aq NH_4Cl and extracted with Et_2O (3 × 10 mL). The solvent was removed under reduced pressure and the crude product purified by flash column chromatography (silica gel; petroleum ether/AcOEt 9/1) to give 1,3-dihydrobenzo[*c*]furan **3r**.

(1*R,1′*R**)-(3,3-Dimethyl-1,3-dihydrobenzo[*c*]furan-1-yl)phenylmethanol (3q):** white solid; mp 67−68 °C (hexane); 70%, dr > 98/2; ^{1}H NMR (500 MHz) 1.51 (s, 3 H), 1.61 (s, 3 H), 3.14 (br s, exchanges with D_2O, 1 H), 4.59 (d, J = 7.3 Hz, 1 H), 5.29 (d, J = 7.3 Hz, 1 H), 6.33 (d, J = 7.9 Hz, 1 H), 7.07−7.12 (m, 2 H), 7.25−7.28 (m, 1 H), 7.37−7.41 (m, 5 H); ^{13}C NMR (125 MHz) 29.5, 30.2, 78.3, 85.7, 85.9, 120.5, 122.7, 127.0, 128.0, 128.1, 128.3, 128.33, 136.9, 139.4, 147.5; GC−MS (70 eV) *m*/*z* 237 (M^+ − OH, 2), 147 (100), 129 (34), 105 (5), 77 (8); FT-IR (KBr, cm^{-1}) 3445, 2966, 1454, 1330, 1150, 1069, 1010, 894, 760, 701.

(1*R,1′*R**,3′*S*)- and (1*R**,1′*R**,3′*R*)-(3-*tert*-Butyl-1,3-dihydrobenzo[*c*]furan-1-yl)phenylmethanol (3r):** colorless oil; inseparable mixture of diastereoisomers; 56% overall yield, dr 1/1; ^{1}H NMR (500 MHz) δ 0.97 (s, 9 H), 1.10 (s, 9 H), 1.63 (br s, exchanges with D_2O, 2 H), 4.51 (d, J = 7.3 Hz, 1 H), 4.66 (d, J =

7.9 Hz, 1 H), 4.98 (d, J = 3.3 Hz, 1 H), 5.00 (s, 1 H), 5.21 (d, J = 7.3 Hz, 1 H), 5.34 (dd, J = 7.3, 3.3 Hz, 1 H), 6.25 (d, J = 7.9 Hz, 1 H), 6.36 (d, J = 7.9 Hz, 1 H), 7.06−7.14 (m, 4 H), 7.21−7.28 (m, 4 H), 7.32−7.47 (m, 8 H); ^{13}C NMR (125 MHz) δ 25.6, 26.3, 35.5, 36.9, 77.9, 78.0, 86.2, 87.0, 91.2, 91.5, 122.4, 122.6, 122.7, 122.9, 126.6, 126.9, 127.1, 128.1, 128.30, 128.31, 128.45, 129.4, 138.8, 138.9, 139.0, 139.3, 140.6, 140.9; GC−MS (70 eV) m/z diastereoisomer with t_R = 11.70 min 264 ($M^+ - H_2O$, 2), 207 (8), 175 (100), 157 (44), 142 (15), 119 (24), 77 (10); diastereoisomer with t_R = 12.07 min 264 ($M^+ - H_2O$, 2), 207 (9), 175 (100), 157 (51), 142 (19), 119 (23), 77 (12); FT-IR (film, cm^{-1}) 3423, 3031, 2956, 2921, 1596, 1458, 1039, 763, 750.

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Supporting Information Available: General experimental methods (S2); spectroscopic data for compounds **1e**, **2d**, **3b**−**c**,**e**−**p** (S3−S12); copies of ^{1}H or ^{13}C NMR spectra for compounds **1e**, **2d**, **3e**, (1*R**,1′*S**,3′*R**)- and (1*R**,1′*S**,3′*S**)-**3f**, (1*R**,1′*S**,3′*R**)- and (1*R**,1′*S**,3′*S**)-**3h**, **3i**,**j**, (1*R**,3*R**)- and (1*R**,3*S**)-**3k**, (1*R**,1′*S**,3′*R**)- and (1*R**,1′*S**,3′*S**)-**3l**, and **3m**−**r** (S14−S32). ORTEP view (S13) and CIF file for compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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