JOC Notes

Preparation of Bicyclo[3.2.0]heptane-2-*endo*,7-*endo*-diols: 1,3-Diols with a Chiral Rigid Backbone†

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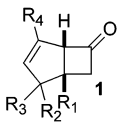
Abstract: The easily available bicyclo[3.2.0]hept-3-en-6-ones (**1a**−**f**) have been converted into the corresponding bicyclo[3.2.0]heptane-2-*endo*,7-*endo*-diols (**4a**−**f**) in an efficient and stereoselective fashion. This preparation opens a route to a family of 1,3-diols with a chiral rigid backbone, potentially suitable as nonracemic precursors for bidentate ligands in asymmetric synthesis.

Bicyclo[3.2.0]hept-3-en-6-ones (**1**) are valuable compounds available through practical and efficient procedures on either the laboratory[1] or industrial scale.[2]

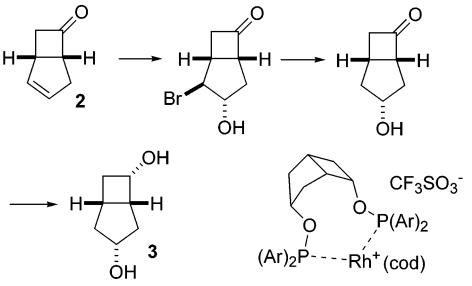


1a: R_1,R_4 = H; R_2,R_3 = CH_3
1b: R_1,R_2,R_3 = H; R_4 = CH_3
1c: R_1,R_4 = CH_3; R_2,R_3 = H
1d: R_1,R_2,R_3,R_4 = H
1e: R_1 = CH_3; R_2,R_3,R_4 = H
1f: R_1,R_3,R_4 = H; R_2= CH_2OBn

Their peculiar wedge-shaped structure, consisting of two condensed rings with different sizes and functional groups, make them useful as versatile intermediates in organic synthesis by allowing straightforward chemoselective, regioselective, and stereoselective manipulations. Grandisol and lineatin,[3] filifolone,[4] raikovenal,[5] and unsaturated bicyclic lactones[4,6,7] have been prepared by using this family of precursors. More recently, the "bicyclo[3.2.0]hept-3-en-6-one approach"[1b] has been extended to the synthesis of important intermediates for primary prostaglandins.[8] Also, an efficient procedure has been devised to effect the resolution and the absolute configuration assignment of the corresponding *endo*-alcohols, easily available by a highly stereoselective reduction.[9] Moreover, parallel studies were performed to successfully achieve the microbial kinetic resolution of racemic mixtures of the ketones and the alcohols.[10] Besides the fast and spectacular progress in the asymmetric synthesis using organometallic reagents,[11] a clear understanding of the origin of enantioselectivity is still to be achieved for many asymmetric reactions. There still is a need for chiral, nonracemic scaffolds suitable for systematic structural changes to produce the broadest possible electronic and stereochemical diversity. These systematic variants would facilitate the analysis of the ligand−metal−substrate interactions that may be responsible for enantioselection.

Recently, our attention was attracted by the results of Roberts and co-workers.[12] They prepared the enantiopure 1,4-bis-phospinite ligands with a bicyclo[3.2.0]heptane backbone for rhodium-catalyzed asymmetric hydrogenation of α-acetamidocinnamic acid derivatives affording enantioenriched (*R*)-phenylalanines (Scheme 1).

SCHEME 1



† Dedicated to Prof. Luciano Caglioti.

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SCHEME 2

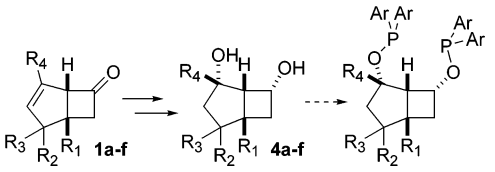


TABLE 1. Stereoselective Preparation of Racemic *endo*-Alcohols 5 and Their Conversion to the Corresponding Boc Derivatives 6

entry	substrate	*endo*-alcohol (yield, %)	Boc,derivative (yield, %)
1	**1a**	**5a** (91)	**6a** (70)
2	**1b**	**5b** (91)	**6b** (74)
3	**1c**	**5c** (90)	**6c** (60)
4	**1d**	**5d** (92)	**6d** (76)
5	**1e**	**5e** (98[a])	**6e** (91)[b]
6	**1f**	**5f**[c] (99)	**6f**[c] (70)

[a] endo: 88%; exo: 8%. [b] Referenced to crude product. [c] Exo/endo = 3:1.

The major limitation of Roberts' approach is that the synthetic scheme is "one-target oriented". The bicyclo-[3.2.0]hept-2-en-6-one is the only easily available member of this family of bicycloketones, and thus the efficiency of the possible ligands may be tuned and optimized by changing *only* the aryls of phosphinite groups.

Therefore, we were attracted by the possibility of using bicyclo[3.2.0]hept-3-en-6-ones (**1**) to prepare a set of chiral bidentate, nonracemic ligands with a diversely substituted bicyclo[3.2.0]heptane framework (**4**). These new ligands will be characterized by an *endo*,*endo*-1,3 relationship of the hydroxyl groups, nested in a four contiguous chirality center cavity (Scheme 2). The aim of the present study is not only to prepare another asymmetric catalytic system but also to improve the understanding of the factors in chiral ligand design concerning the bicyclo[3.2.0]heptane backbone by exploring a variety of possible derivatives and chiral ligand modifications.

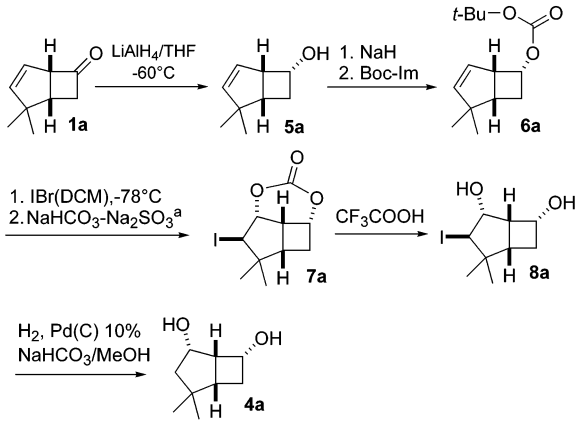
Herein, we report a successful preparation of significant representatives of this class of diols. Our task has been the search for an efficient and general procedure for the conversion of bicyclo[3.2.0]hept-3-en-6-ones (**1**) into bicyclo[3.2.0]heptane-2-*endo*,7-*endo*-diols (**4**).

We previously observed that the wedge shape of bicylic compounds **1** allows a highly stereoselective reduction of the carbonyl group by treatment with lithium aluminum hydride in tetrahydrofuran (THF) at low temperature. The desired *endo*-alcohols **5** were obtained in excellent yields (Table 1) when the reduction was carefully performed at −60 °C allowing the temperature to rise slowly to ambient temperature before quenching.

Bicyclic *endo*-alcohols **5** became the key precursors for the regio- and stereospecific functionalization of the carbon,carbon double bond of the five-membered ring. In fact, we considered that the C6 *endo* hydroxy group could play a pivotal role in the hydroxylation of the double bond through an intramolecular reaction. Scheme 3 depicts the synthetic scheme of the general procedure applied to bicyclic ketone **1a**.

endo-Alcohols **5a**−**f** were converted into the corresponding *tert*-butyl carbonates **6a**−**f** in fair to good yields

SCHEME 3[a]



[a] Key: 1:1 solution of $NaHCO_3$ 5%/Na_2SO_3 20%.

TABLE 2. Stereospecific Iodocarbonatation, Hydrolysis, and Hydrogenolysis of Boc Derivatives 6a−f

entry	Boc derivative	iodocarbonate (yield, %)	iodo diol (yield, %)	*endo*,*endo*-diol (yield, %)
1	**6a**	**7a** (90)	**8a** (60)	**4a** (65)
2	**6b**	**7b**[a]	**8b** (66)	**4b** (72)
3	**6c**	**7c**[a]	**8c** (67)	**4c** (75)
4	**6d**	**7d**[a]	**8d** (70)	**4d** (63)
5	**6e**	**7e**[a]	**8e** (88)	**4e** (99)
6	**6f**[b]	**7f**[a]	**8f**[c] (65)	**4f**[c] (92)

[a] Not isolated. [b] exo/endo = 3:1.

by reaction of the sodium alkoxide with Boc-Im (Table 1). Then, a totally regio- and stereocontrolled iodocarbonate cyclization of compound **6a** occurred when induced by iodine monobromide (IBr) in dichloromethane (DCM) according to the procedure developed by Duan and Smith.[13,14]

Though cyclic iodocarbonate **7a** could be isolated in good yield, we observed that these intermediates sometimes undergo occasional decomposition during the purification. To avoid this risk, crude iodocarbonates **7b**−**f** were converted in situ into the corresponding iododiols **8b**−**f** by hydrolysis with trifluoroacetic acid (Table 2).

Finally, these latter compounds gave the 2-*endo*,7-*endo*-diols **4a**−**f** by palladium-catalyzed hydrogenolysis in the presence of sodium hydrogen carbonate. The yields reported in Tables 1 and 2 are referenced to products isolated and purified by flash chromatography.

The relative configurations of the intermediates as well as of the final products were determined spectroscopically (see the Supporting Information). Moreover, the X-ray crystal structural analyses of compound **8c** clearly indicate the *endo*,*endo* relationship of the hydroxyl groups, both opposite to the *exo*-iodine on C3 (Figure 1).[15]

We then faced the preparation of an enantiopure representative of bicyclo[3.2.0]heptane-2-*endo*-7-*endo*-diols. In doing so, we tried to improve the procedure to have a faster, more compact synthetic scheme. The

(13) Duan, J. J.-W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703.
(14) The carbonate moiety acts as a temporary tether. The reaction generates two new stereo centres in one step, through an intramolecular process.
(15) Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC number 227177.

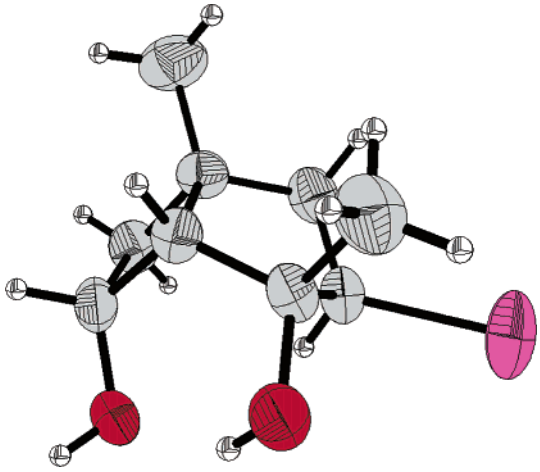
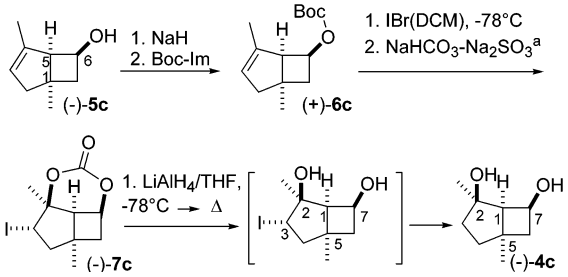


FIGURE 1. X-ray structure of compound **8c**.

SCHEME 4[a]



[a] Key: 1:1 solution of $NaHCO_3$ 5%/Na_2SO_3 20%.

bicyclic *endo*-alcohol **5c** played as benchmark. It was resolved by using (−)-camphanic acid chloride as the resolving agent.

Then, compound (−)-(1*R*,5*S*,6*S*)-**5c**[9] was converted into the corresponding *tert*-butyl carbonate (+)-**6c** ($[\alpha]_D$ +126.9, *c* 1.61, $CHCl_3$) that gave the iodocarbonate (−)-**7c** ($[\alpha]_D$ −33.7, *c* 1.22, $CHCl_3$) by reaction with IBr. Treatment with $LiAlH_4$ in THF at −70 °C gave rise to a fast carbonate reduction to give the intermediate iododiol **8c** that could be isolated and purified. However, if the reaction was protracted for several hours at room temperature or at 50 °C, a slow hydrodeiodination occurred affording the desired *endo*,*endo*-diol (−)-(1*S*,2*R*,5*R*,7*S*)-**4c** ($[\alpha]_D$ −33.8, *c* 1.09, $CHCl_3$) in a 35% overall yield from the *endo*-alcohol **5c** (Scheme 4).

In conclusion, we have developed a simple and efficient methodology for the preparation of a variety of bicyclo-[3.2.0]heptane-2-*endo*,7-*endo*-diols with high regio- and stereoselectivity. This route will be extended to the preparation of enantiomerically pure representatives of a new and large family of bidentate ligands having the bicyclo[3.2.0]heptane as common backbone. Our goal is to try these new compounds in a wide variety of enantioselective reactions and to start studies on the structure-efficiency relationship by exploiting the many points of diversity that this bicyclo[3.2.0]heptane framework offers.

Experimental Section

Procedure for the Synthesis of BOC Derivatives 6. NaH (50% w/w; 0.288 g; 3 equiv) was washed, under nitrogen atmosphere, with anhydrous petroleum ether (2 × 5 mL). After removal of the solvent, 6 mL of anhydrous THF was added and the mixture was cooled to −10 °C. Keeping the temperature under −5 °C, a solution of the alcohol (2 mmol dissolved in 6 mL of THF) was slowly dropped into the suspension. After 30 min (when the development of gases was ceased), a solution of BOC-imidazole (0.530 g, 1.05 equiv, dissolved in 4 mL of THF) was dropped into the reaction mixture, without exceeding 0 °C. The reaction was monitored by TLC and stopped after the disappearance of the starting material. The reaction mixture was diluted with pentane, and the solid imidazole precipitated during the reaction was filtered on a Celite pad, washing the solid residue twice with pentane. The organic solution obtained was washed with water (2 × 5 mL) and brine (1 × 5 mL) and dried over $MgSO_4$. After evaporation of the solvent, a crude oil was obtained. Pentane was added (6 mL), and a solid precipitate of imidazole was formed. The mixture was filtered, and after evaporation of the solvent the procedure was repeated until no more solid was formed after the addition of pentane. The crude BOC derivatives were obtained in quantitative yields; all the crude products contained small traces of BOC-imidazole (max 2−3%) and were used as such for the following reactions. Analytical samples were obtained by flash chromatography. For spectroscopic and analytical data of compounds **6a**−**f**, see the Supporting Information.

Procedure for the Synthesis of Iodo Diols 8. A solution of the BOC-derivative (1 mmol in 11 mL of DCM) was cooled, under N_2 atmosphere, to −78 °C. A solution of IBr (1.8 mmol in 5 mL DCM) was slowly dropped into the reaction mixture, keeping the temperature around −70 °C. The reaction was kept in the dark until the disappearance of the starting material as monitored by TLC. The mixture was then diluted with Et_2O, and 6 mL of a 1:1 solution of $NaHCO_3$ 5%/Na_2SO_3 20% was added. The mixture was warmed to 0 °C and stirred at this temperature for 15−20 min until the organic phase turned colorless or pale yellow. The organic solution obtained was washed with brine (1 × 5 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude iodocarbonate derivatives were obtained in quantitative yields and were used as such for the following reactions. For **7a**, an analytically pure sample was obtained as reported below. The crude oil obtained was dissolved in 1.2 mL of THF, and 1.2 mL of H_2O was added. The mixture was cooled to 0 °C, and 0.23 mL of CF_3COOH was added. The reaction was then warmed to room temperature and monitored by TLC (DCM/Et_2O 5:1) until disappearance of the starting material. The reaction mixture was diluted with DCM and neutralized, adding a $NaHCO_3$ satd solution until effervescence ceased. The organic solution obtained was washed with brine (1 × 5 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude iodo diol derivatives were obtained in the yields reported for each product. For spectroscopic and analytical data of compounds **8a**−**f**, see the Supporting Information.

Procedure for the Preparation of Racemic Diols 4. A solution of the starting iodo diol (1 mmol) in methanol (10 mL) in a steel autoclave was flushed with argon. To this solution were then added 10% Pd/C (37 mg) and solid K_2CO_3 (140 mg). The mixture was then stirred under 5 atm of hydrogen for 48 h. After this time, TLC analysis showed a complete reaction. The mixture was filtered on a Celite pad and washed with methanol. After the solvent was evaporated under moderate vacuum, the residue was partitioned between methylene chloride and water. The aqueous layer was back-extracted with more methylene chloride. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated under moderate vacuum. Most of the crude materials were found to be pure enough by NMR analysis. When needed they can be purified by chromatography over a short pad of silica gel.

4,4-Dimethylbicyclo[3.2.0]heptane-2,7-diol (4a). Colorless oil. TLC (Et_2O): R_f 0.52 UV−vis and Ce(IV). ^1H NMR δ (ppm): 4.80−4.65 (bs, 2H); 4.55 (m, 1H); 4.35 (m, 1H); 2.88 (m, 1H); 2.55 (m, 1H); 1.90−1.60 (m, 4H); 0.80 (s, 3H); 0.70 (s, 3H). ^{13}C NMR δ (ppm): 77.0; 65.6; 47.4; 44.1; 41.5; 40.0; 33.7; 28.3; 22.9. IR (neat): 3318; 2954; 1465, 1127, 1115, 1068. *m*/*z*: 138 (10); 123 (14); 95 (97); 73 (48); 69 (45); 41 (100). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.81; H, 10.22.

2-Methylbicyclo[3.2.0]heptane-2,7-diol (4b). Colorless oil. TLC (DCM/Et_2O 5:1) R_f 0.2, Ce(IV). ^1H NMR δ (ppm): 4.80 (bs, 2H); 4.35 (m, 1H); 2.50 (m, 1H); 2.38 (m, 1H); 2.20 (m, 2H); 1.7−1.4 (m, 4H); 1.10 (s, 3H). ^{13}C NMR δ (ppm): 83.0; 65.6; 50.2; 40.1; 36.8; 31.4; 30.4; 29.1. IR (neat): 3314; 2947; 1179, 1115, 1094. *m*/*z*: 124 (15); 109 (28); 87 (56); 81 (100); 67 (21); 53 (21). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.48; H, 9.93.

2,5-Dimethylbicyclo[3.2.0]heptane-2,7-diol (4c). White solid. Mp: 52−53 °C. TLC (DCM/Et_2O 5:1) R_f 0.19 Ce(IV). ^1H NMR δ (ppm): 4.54 (bs, 2H), 4.46 (q with further fine couplings, 1H, J = 6.9 Hz), 2.31−2.10 (m, 2H), 2.01 (d with further fine couplings, 1H, J = 8.2 Hz,), 1.91−1.81 (dd, 1H, J = 12.9, 6.6 Hz), 1.79−1.69 (dd, 1H, J = 12.4, 6.6 Hz), 1.57−1.46 (dd, 1H, J = 12.6, 6.9 Hz), 1.42−1.28 (m, 1H), 1.15 (s, 3H), 1.05 (s, 3H). ^{13}C NMR δ (ppm): 82.9, 63.9, 55.2, 42.5, 41.2, 39.1, 38.3, 29.4, 26.8. I. R. (KBr): 3221, 2921, 1446, 1368, 1284, 1166, 1062, 1035, 968. *m*/*z*:138 (7), 123 (9), 97 (69), 95 (78), 87 (41), 67 (27), 55 (29), 43 (100), 41 (58). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.25; H, 10.42.

Bicyclo[3.2.0]heptane-2,7-diol (4d). Pale yellow oil. TLC (DCM/Et_2O 5:1) R_f 0.20 Ce(IV). ^1H NMR δ (ppm): 4.52 (bs shifting, 2H), 4.40 (q, 1H, J = 7.8 Hz), 4.32 (q, 1H, J = 8.1 Hz), 2.83−2.72 (m, 1H), 2.52 (dtd, 1H, J = 12.8, 8.8, 2.5 Hz), 2.22 (quin, 1H, J = 6.9 Hz), 2.13−1.92 (m, 2H), 1.72−1.42 (m, 3H). ^{13}C NMR δ (ppm): 78.2, 66.1, 44.1, 37.2, 34.1, 30.4, 30.3. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.49; H, 9.48. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.80; H, 10.02.

5-Methylbicyclo[3.2.0]heptane-2,7-diol (4e). Pale yellow oil. TLC (DCM/Et_2O 5:1) R_f 0.19 Ce(IV). ^1H NMR δ (ppm): 4.47 (q, 1H, J = 8.0 Hz), 4.41−4.23 (q superimposed with a shifting bs, 3H, J = 8.2 Hz), 2.36 (td, 1H, J = 8.0, 2.4 Hz), 2.22−2.00 (m, 3H), 1.90−1.80 (dd, 1H, J = 12.6, 6.9 Hz), 1.56−1.47 (dt, 1H, J = 12.5, 3.9 Hz), 1.38−1.21 (m 1H), 1.06 (s, 3H). ^{13}C NMR δ (ppm): 78.0, 64.4, 48.7, 42.9, 38.2, 38.1, 35.3, 26.2. IR (neat): 3331, 2947, 1450, 1118, 1074, 1048. *m*/*z*: 124, 109, 83, 81, 55, 41. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.51; H, 9.99.

Preparation of the Enantiomerically Pure Ligand (−)-4c. Alcohol **5c** was resolved according to a method we already described.[9] It was then quantitatively converted to the corresponding BOC derivative (+)-(1*R*,5*S*,6*S*)-**6c**, $[\alpha]^{21}_D$ +126.9 (*c* 1.61, $CHCl_3$), according to the method described above. Carbonate (+)-**6c** (3.56 g; 14.94 mmol) was then subjected to the iodocarbonatation as described above, and the crude iodocarbonate (−)-**7c**, $[\alpha]^{20}_D$ −33.7 (*c* 1.22, $CHCl_3$), was immediately taken to the following reduction. A solution of the crude iodocarbonate (−)-**7c** (1.29 g, 4.19 mmol) in THF (5 mL) was cooled to −78 °C. $LiAlH_4$ (1 M in THF, 10.5 mL, 10.5 mmol) was then added dropwise. After the addition was complete, the cooling bath was removed and the mixture allowed to warm to room temperature and left stirring overnight. The reaction was quenched by the careful addition of sat. NH_4Cl and the mixture extracted with 3 × 20 mL of Et_2O. The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness. The crude material was purified by flash chromatography (DCM/Et_2O 5:1) to afford 0.818 mg (35% yield from **5c**) of a white solid. Mp: 56−58 °C. $[\alpha]^{20}_D$: −33.8 (*c* 1.09, $CHCl_3$). ^1H NMR δ (ppm): 1.07 (s, 3H); 1.14 (s, 3H); 1.33−1.39 (m, 1H); 1.48−1.55 (dd, 1H, J = 6.6, 12.9 Hz); 1.71−1.77 (dd, 1H, J = 6.6, 12.4 Hz); 1.82−1.89 (dd, 1H, J = 6.9, 13.5 Hz); 2.02 (bd, 1H); 2.11−2.29 (m, 2H); 4.46 (q, with further fine couplings, 1H, J = 8.5 Hz); 4.96 (bs, 1H). ^{13}C NMR δ (ppm): 26.6; 29.2; 38.1; 38.9; 41.0; 42.3; 55.0; 63.7; 82.7. IR (KBr): 3239, 2937, 1458, 1377, 1291, 1166, 1084, 1046, 968. *m*/*z* (ES+): 179, 157; (ES-): 156, 155. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.18; H, 10.30.

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Supporting Information Available: ^{13}C NMR spectra of compounds **4a**−**f**, **6a**−**f**, **7a**, and **8a**−**f**; X-ray crystal data of compound **8c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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