JOC*Note*

Enantioselective Synthesis of Bridged Bicyclic Ring Systems

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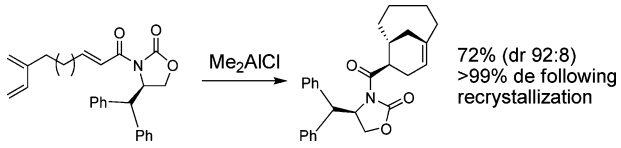

The type 2 intramolecular Diels−Alder (IMDA) reaction is a valuable method for synthesis of both carbocyclic and heterocyclic bridged bicyclo[5.3.1]undecane and bicyclo[4.3.1]-decane ring systems. These structures are common to a number of biologically important natural products. Asymmetric variants of the type 2 IMDA reaction incorporating oxazolidinone chiral auxiliaries have been evaluated. This study has resulted in systems that deliver bridged bicyclic [5.3.1] and [4.3.1] ring systems in high diastereomeric (97−99% de) and enantiomeric purity.

The type 2 intramolecular Diels−Alder (IMDA) cycloaddition is arguably the most efficient method to assemble bridged bicyclic rings.[1] These structures are found in a number of biologically important natural products including CP-225,917 (**1**),[2] esperamicin (**2**),[3] and paclitaxel (Taxol) (**3**).[4] Derivatives of bicyclo[5.3.1]undecane **4** and bicyclo[4.3.1]decane **5** are the most common naturally occurring bridged bicyclics. The type 2 IMDA synthesis of these ring systems occurs with predictable and complete regio- and stereochemical selectivity. Despite this favorable aspect of the reaction, the synthetic utility remains limited due to the inability to control the absolute configuration of the cycloadduct. Recent approaches to remedy this limitation have appeared.[5] In this note, we demonstrate the ability to control diastereoselectivity in the type 2 IMDA reaction through the use of chiral auxiliaries. A transition state model has been proposed and confirmed, permitting synthesis with a predictable stereochemical outcome.

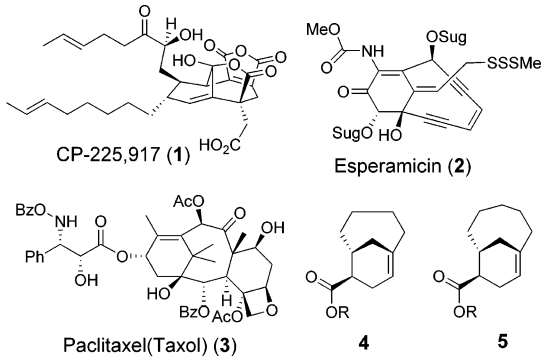

FIGURE 1. Carbocycles **4** and **5** and examples of natural products possessing bridged bicyclic structures.

Chiral oxazolidinone auxiliaries incorporated in dienophiles have influenced diastereoselectivity in Diels−Alder cycloadditions. For example, Evans and co-workers have reported that chiral α,β-unsaturated *N*-acyloxazolidinones coordinated to dialkylaluminum chloride catalysts are highly reactive and highly diastereoselective dienophiles in Diels−Alder reactions.[6] They also described the successful extension of this methodology to type 1 IMDA reactions. Following Lewis acid coordination, the dienophile interacts preferentially with the diastereotopic face of the diene that is opposite the bulky oxazolidinone substituent.[6] In view of these reports, we screened oxazolidinone derivatives to examine their effect on the type 2 IMDA reaction.

In exploring the effectiveness of chiral oxazolidinones for influencing the diastereoselectivity of the type 2 IMDA reaction, we focused on the asymmetric formation of carbocycles **4** and **5** (Figure 1). Bicyclo[4.3.1.]decane **4** and bicyclo[5.3.1]undecane **5** were deemed appropriate platforms for evaluating the capabilities of oxazolidinone auxiliaries since this reaction has been used in the assembly of advanced intermediates of esperamicin (**2**)[3] and paclitaxel (**3**)[4] and for the total synthesis of CP-225,917 (**1**).[2] Methods for the stereoselective formation of these ring systems can provide tools for the enantiopure synthesis of natural products and analogues that contain these bridged bicyclic systems.

Known aldehydes **6** and **7**[7] were used as the components in the synthesis of the type 2 IMDA reaction precursors (Scheme 1). A Horner−Wadsworth−Emmons reaction was employed

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SCHEME 1. Synthesis of Oxazolidinone Appended Trienes

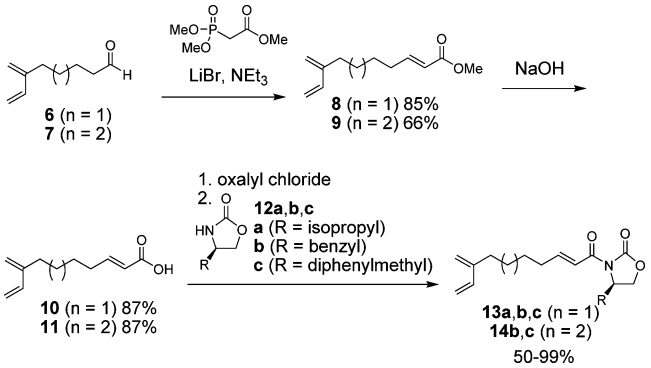
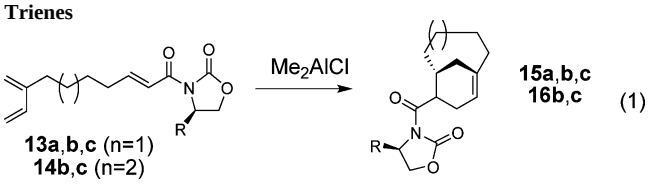


TABLE 1. Type 2 IMDA Reaction of Oxazolidinone Appended Trienes



entry	triene	product	temp (°C)	time (h)	% yield	dr[a]
1	**13a**	**15a**	0	5	76	58:42
2	**13b**	**15b**	0	5	83	83:17
3	**13b**	**15b**	−78	96	10	87:13
4	**13c**	**15c**	0	5	72[b]	92:8
5	**14b**	**16b**	0	7	46[c]	83:17
6	**14c**	**16c**	rt	3	71[d]	94:6

[a] Diastereomeric ratio (dr) established by ^{1}H NMR of crude product. [b] Based on recovery of unreacted **13c**. [c] Based on recovery of unreacted **14b**. [d] Based on recovery of unreacted **14c**.

using trimethylphosphonoacetate and triethylamine in the presence of lithium bromide to generate (*E*)-triene esters **8** and **9** from aldehydes **6** and **7**. These esters were hydrolyzed with aqueous NaOH to form acids **10** and **11**. Synthesis of the oxazolidinone appended trienes **13a**−**c** and **14b**,**c** was accomplished by treating acids **10** and **11** with oxalyl chloride to form the corresponding acid chlorides that were treated with the lithium amides of oxazolidinones **12a**−**c**. The absolute configuration of these oxazolidinone derivatives was *R*.

Diastereoselectivity in the Me_2AlCl-mediated type 2 IMDA reaction of trienes **13a**−**c** and **14b**,**c** was evaluated, and the results are compiled in Table 1. The cycloadducts were formed in moderate to good yields with varying diastereoselectivity. The diastereomeric ratios (dr) of the mixtures were determined by ^{1}H NMR of the crude product. 4-Diphenylmethyl-2-oxazolidinone (**12c**) imparted the greatest degree of selectivity for both carbocycles. Bicyclo[4.3.1]decane **15c** and bicyclo[5.3.1]-undecane **16c** were formed from triene **13c** in 72% yield (92:8 dr) and triene **14c** in 71% yield (94:6 dr), respectively. Single recrystallization of the diastereomeric mixture yielded the major isomer of **16c** in 91% recovery (>96% de). The minor diastereomer of **15c** was not detectable by ^{1}H NMR following single recrystallization of the diastereomeric mixture (95% recovery). Diastereomeric ratios were comparable between the bicyclo[4.3.1]decane cycloadducts **15** and the bicyclo[5.3.1]-undecane cycloadducts **16** when the oxazolidinone employed in the cycloaddition was identical.

Slightly higher diastereoselectivity was observed at lower temperatures. However, these reactions proceeded slowly.

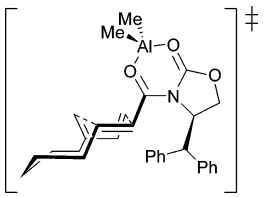


FIGURE 2. Proposed transition state.

Compound **15b** was formed in only 10% yield (dr 87:13) after stirring triene **13b** for 96 h at −78 °C in the presence of dimethylaluminum chloride (entry 3). However, when the reaction was performed at 0 °C, the reaction rate increased without significant erosion in diastereoselectivity (entry 2). It should be noted that trienes **14b** and **14c** require longer reaction times or higher temperatures. This observation reflects the higher activation energy ($\Delta G^{\ddagger}$) for formation of the [5.3.1] ring system relative to the [4.3.1] ring system. The difference in free energy of activation has been attributed to differences in the entropy of activation between the two reactants, presumably due to the longer dienophile−diene linker.[8]

The predictable and complete control of both regio- and stereochemistry in the type 2 IMDA has been attributed to constraints imposed by the connectivity of the reacting components. In this context, it is understood that the origins of selectivity are due more to mechanical constraints (meta or 1,3-regioselectivity and tether endo stereochemistry) that limit the available transition states rather than frontier molecular orbital interactions that are typically invoked to account for observed selectivity. The limited number of transition state configurations available for this reaction simplifies the formulation of a working model that predicts the diastereoselectivity of the reaction. The proposed transition state for the intramolecular cycloaddition of Diels−Alder precursor **13c** incorporating the *R* configuration of the chiral auxiliary is shown in Figure 2. The model imposes the meta regiochemistry and the tether endo configuration. It is also assumed that the α,*β*-unsaturated carbonyl group resides in the *s*-cis conformation to avoid nonbonded steric interactions between the alkene and the oxazolidinone. This assumption is consistent with the observation that α,*β*-unsaturated amides preferentially reside in the *s*-cis conformation.[9] Another aspect of this model is the association of Me_2AlCl with the triene in a bidentate fashion. This coordination locks the molecule into a rigid structure with a well-defined chiral environment. The diene approaches the dienophile preferentially from the C_α-si face because the opposing face is congested by the presence of the diphenylmethyl substituent of the oxazolidinone auxiliary.[6] This model predicts the *R* configuration of the new asymmetric bridgehead carbon when the oxazolidinone auxiliary has the *R* configuration. X-ray crystallography of bicyclic compound **15c** supports the proposed model. The absolute configuration of the oxazolidinone stereocenter in compound **15c** was *R*, and therefore the newly formed bridgehead stereocenter has the *R* configuration.

Structural similarities between compound **15c** and **16c** imply that the model can also predict the absolute stereochemistry of

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compound **16c**. The optical rotations of **15c**, $[\alpha]^{23}_D$ −137.0 (*c* 0.9, $CHCl_3$), and **16c**, $[\alpha]^{24}_D$ −116.4 (*c* 0.8, $CHCl_3$), indicate that chiral environment of the two are comparable. Furthermore, these two compounds have similar ^{1}H NMR spectra. On the basis of these observations, it can reasonably be assumed that compounds **15c** and **16c** have the same absolute configuration and, furthermore, that the model also predicts the absolute stereochemistry of the [5.3.1] cycloadduct **16c**.

In summary, type 2 IMDA reaction of trienes **13a**−**c** and **14b**,**c** using excess Me_2AlCl as a Lewis acid catalyst produced bicyclo[4.3.1]decane compounds **15a**−**c** and bicyclo[5.3.1]-undecane compounds **16b**,**c** in moderate to good yields. The diastereomeric ratio of the cycloadducts varied depending on the oxazolidinone auxiliary. 4-Diphenylmethyl-2-oxazolidinone (**12c**) provided the greatest degree of selectivity (94:6). Recrystallization of the cycloadducts afforded the [5.3.1] and [4.3.1] bridged bicyclic rings systems in high diastereomeric (97−99% de) and high enantiomeric purity. For the [4.3.1] compound, the minor diastereomer was undetectable by ^{1}H NMR following recrystallization. A transition state model has been proposed for the cycloaddition that correctly predicts the stereochemistry of the cycloaddition.

Experimental Section

(*E*)-Methyl 8-methylene-2,9-decadienoate (8). To a stirred solution of lithium bromide (215 mg, 2.47 mmol) in 28 mL of THF was added trimethylphosphonoacetate (450 mg, 2.47 mmol). The mixture was stirred for 5 min, and triethylamine (500 mg, 5.6 mmol) was added. The resulting mixture was stirred for 10 min, and 6-methylene-7-octen-1-al (**6**) (340 mg, 2.47 mmol) was added. The solution was stirred overnight and diluted with a solution of saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by silica gel flash chromatography using hexanes/ethyl acetate (99:1) to yield 407 mg (85%) of **8** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (dt, J = 14.1, 7.0 Hz, 1H), 6.36 (dd, J = 17.6, 10.8 Hz, 1H), 5.84 (dt, J = 14.1, 1.6 Hz, 1H), 5.21 (d, J = 17.6 Hz, 1H), 5.05 (d, J = 10.8 Hz, 1H), 5.01 (d, J = 1.2 Hz, 1H), 4.97 (s, 1H), 3.73 (s, 3H), 2.22 (m, 4H), 1.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 149.6, 146.3, 139.1, 121.2, 116.0, 113.4, 51.6, 32.3, 31.3, 28.1, 27.8; IR (NaCl film) 3089, 2937, 2860, 2361, 1728, cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O$ $(M)^+$ 194.1307, observed 194.1308.

(*E*)-Methyl 9-methylene-2,10-undecadienoate (9). To a solution of lithium bromide (914 mg, 10.5 mmol) in 3.7 mL of THF was added trimethylphosphonoacetate (1.91 g, 10.5 mmol). The mixture was stirred for 5 min, and triethylamine (2.13 g, 21 mmol) was added. The resulting mixture was stirred for 10 min, and 7-methylene-8-nonen-1-al (**7**) (1.6 g, 10.5 mmol) was added. The solution was stirred overnight. A solution of saturated aqueous NH_4Cl was added to the reaction mixture. The mixture was extracted with diethyl ether, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by silica gel flash chromatography using hexanes/ethyl acetate (99:1) to yield 1.45 g (66%) of **9** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (dt, J = 15.5, 7.0 Hz, 1H), 6.36 (dd, J = 17.6, 10.8 Hz, 1H), 5.84 (dt, J = 15.6, 3.1 Hz, 1H), 5.22 (d, J = 17.6 Hz, 1H), 5.05 (d, J = 10.9 Hz, 1H), 5.00 (s, 1H), 4.97 (s, 1H), 3.73 (s, 3H), 2.21 (m, 4H), 1.53−1.45 (m, 4H), 1.39−1.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 149.6, 146.2, 138.9, 120.9, 115.7, 113.2, 51.7, 32.5, 31.6, 29.4, 28.3, 28.2; IR (NaCl film) 3086, 2933, 2858, 1724, 1656, 1594 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O$ $(M)^+$ 208.1463, observed 208.1463.

(*E*)-8-Methylene-2,9-decadienoic acid (10). To a solution of (*E*)-methyl 8-methylene-2,9-decadienoate (**8**) (54 mg, 0.28 mmol) in 2 mL of THF was added 2 mL of aqueous 1.5 N sodium hydroxide. The mixture was heated at 70 °C for 8 h, cooled to rt, diluted with 8 mL of saturated aqueous sodium bicarbonate, and washed with 10 mL of diethyl ether. The aqueous layer was cooled to 0 °C and acidified to pH 1 with 6 N hydrochloric acid. The mixture was extracted with 50 mL of CH_2Cl_2, and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 44 mg (87%) of **10** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dt, J = 15.6, 7.0 Hz, 1H), 6.41 (dd, J = 17.6, 10.8 Hz, 1H), 5.88 (dt, J = 15.6, 3.1 Hz, 1H), 5.27 (d, J = 17.6 Hz, 1H), 5.11 (d, J = 10.9 Hz, 1H), 5.02 (s, 1H), 4.98 (s, 1H), 2.33−2.26 (m, 4H), 1.66−1.53 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 152.2, 146.0, 138.9, 120.8, 115.9, 113.2, 32.2, 31.1, 27.8, 27.6; IR (NaCl film) 3400, 2934, 1700, 1654, 1420, 1287 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O$ $(M)^+$ 180.1150, observed 180.1157.

(*E*)-9-Methylene-2,10-undecadienoic acid (11). To a solution of (*E*)-methyl methylene-9-methylene-2,10-undecadienoate (**9**) (1.1 g, 5.3 mmol) in 35 mL of THF was added 35 mL of aqueous 1.5 N sodium hydroxide. The mixture was heated at 70 °C for 8 h, cooled to rt, diluted with 30 mL of saturated aqueous sodium bicarbonate, and washed with 60 mL of diethyl ether. The aqueous layer was cooled to 0 °C and acidified to pH 1 with aqueous 6 N hydrochloric acid. The mixture was extracted with 50 mL of CH_2Cl_2, and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to yield 960 mg (87%) of **11** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (dt, J = 15.7, 7.0 Hz, 1H), 6.37 (dd, J = 17.6, 10.8 Hz, 1H), 5.84 (dt, J = 15.7, 3.1 Hz, 1H), 5.22 (dd, J = 17.6, 0.5 Hz, 1H), 5.06 (ddd, J = 10.9, 1.8, 1.2 Hz, 1H), 5.01 (d, J = 1.22 Hz, 1H), 4.98 (d, J = 1.22 Hz, 1H), 2.27−2.20 (m, 4H), 1.55−1.48 (m, 4H), 1.41−1.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 152.8, 146.8, 139.4, 121.2, 116.1, 113.6, 32.7, 31.6, 29.5, 28.3, 28.2; IR (NaCl film) 3092, 2936, 1695, 1648, 1596, 1420, 1285, 1243 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_2$ $(M - H)^+$ 193.1228, observed 193.1231.

General Procedure for the Synthesis of Oxazolidinone Appended Trienes: Preparation of 14c. To a stirred solution of (*E*)-9-methylene-2,10-undecadienoic acid (**11**) (0.544 mmol, 105 mg) in 8 mL of toluene was added oxalyl chloride (0.71 mmol, 61 μL). The mixture was stirred at rt for 17 h and then concentrated in vacuo to a yellow oil that was used in the next step without purification. To a stirred solution of (*R*)-4-(diphenylmethyl)-2-oxazolidinone (**12c**) (0.340, 146 mg) in 1.3 mL of THF at −78 °C was added *n*-butyllithium (0.340 mmol, 0.134 mL, 2.53 M in hexanes). After stirring for 15 min, the acid chloride was added, and the mixture was stirred for 30 min and then warmed to 0 °C and stirred for 15 min. The reaction mixture was quenched by adding 0.2 mL of a saturated aqueous solution of NH_4Cl, and the aqueous layer was extracted with 3 × 10 mL of diethyl ether. The organic extracts were dried over anhydrous $NaSO_4$ and concentrated in vacuo. The resultant oil was purified by silica gel flash chromatography using hexanes/ethyl acetate (15:1) to yield 100 mg (68%) of **14b** as a pale yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39−7.11 (m, 12H), 6.43 (dd, J = 21.0, 13.2 Hz, 1H), 5.42 (m, 1H), 5.28 (d, J = 21.1 Hz, 1H), 5.12 (d, J = 13.0 Hz, 1H), 5.06 (s, 1H), 5.04 (s, 1H), 4.82 (d, J = 6.3 Hz, 2H), 4.53−4.46 (m, 2H), 2.33 (dd, J = 17.0, 8.4 Hz, 2H), 2.27 (t, J = 9.0 Hz, 2H), 1.59−1.54 (m, 4H), 1.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 153.4, 151.9, 146.4, 139.7, 139.0, 138.2, 129.4, 128.9, 128.7, 128.4, 127.6, 127.1, 120.3, 115.7, 113.2, 64.9, 56.4, 50.8, 32.7, 31.3, 29.2, 28.0, 27.9; IR (NaBr pellet) 2927, 1780, 1684, 1654, 1363, 1210 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{31}NO_3$ $(M + Na)^+$ 430.2382, observed 430.2381.

General Procedure for the Type 2 Intramolecular Diels−Alder Reaction: Preparation of 15c. To a stirred solution of (4*R*)-4-(diphenylmethyl)-3-((*E*)-8-methylene-2,9-decadienoyl)-2-oxazolidinone (**13c**) (0.241 mmol, 100 mg) in 24 mL of CH_2Cl_2 at 0 °C was added Me_2AlCl (0.722 mmol, 0.722 mL, 1 M solution in

hexanes). The mixture was stirred at this temperature for 5 h, and then the mixture was poured into 25 mL of 1 N HCl. The aqueous solution was extracted with 2 × 25 mL of CH_2Cl_2, and the organic extracts were dried over anhydrous $NaSO_4$ and filtered. The solution was concentrated in vacuo to an oil that was purified by silica gel flash chromatography using petroleum ether/diethyl ether/ethyl acetate (5:1:0.25) to yield 61 mg (72% based on recovery of 15 mg of unreacted **13c**) of **15c** as a white solid. Recrystallization of the diastereomeric mixture in methanol yielded exclusively the major isomer in 95% recovery (the minor diastereomer was undetectable by ^{1}H NMR). Crystals adequate for X-ray crystallographic analysis were grown by slow diffusion of methanol into a solution of 45 mg of **15c** in 0.25 mL of acetonitrile. Colorless needles were formed after several days: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37−7.15 (m, 10H), 5.57 (m, 1H), 5.38 (m, 1H), 4.70 (d, J = 6.5 Hz, 1H), 4.38 (m, 2H), 3.24 (ddd, J = 10.8, 5.6, 2.9 Hz, 1H), 2.58 (s, 1H), 2.34 (m, 1H), 2.24 (m, 1H), 2.03 (m, 3H), 1.78 (m, 1H), 1.67 (m, 1H), 1.48−1.35 (m, 4H), 1.21 (m, 1H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 176.8, 153.2, 142.9, 139.6, 138.2, 129.3, 129.0, 128.7, 128.6, 127.9, 127.1, 123.3, 65.1, 56.6, 51.5, 45.4, 38.4, 34.9, 34.0, 31.6, 28.6, 26.2, 22.3; IR (NaBr pellet) 3019, 2926, 2853, 1762, 1705, 1451, 1384,1197 cm^{-1}; HRMS (EI) calcd for $C_{27}H_{29}O_3N$ $(M + Na)^+$ 438.2045, observed 438.2035; $[\alpha]^{23}_D$ −137.0 (*c* 0.9, $CHCl_3$); mp 140−141 °C.

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Supporting Information Available: Preparation and characterization data of **13a**−**c**, **14b**, **15a**,**b**, and **16b**,**c**; ^{1}H and ^{13}C NMR spectra of all new compounds; X-ray crystallography data for **15c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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