Metal-Mediated Carbonyl-1,3-butadien-2-ylation by 1,4-Bis(methanesulfonyl)-2-butyne or 1,4-Dibromo-2-butyne in Aqueous Media: Asymmetric Synthesis of 3-Substituted 3-Hydroxy-*β*-lactams

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Metal-mediated 1,3-butadien-2-ylation reactions between 1,4-dibromo-2-butyne or 1,4-bis(methanesulfonyl)-2-butyne and optically pure azetidine-2,3-diones were investigated in aqueous media, offering a convenient asymmetric entry to the potentially bioactive 3-substituted 3-hydroxy-*β*-lactam moiety. The diastereoselectivity of the addition reaction was controlled by the bulky chiral auxiliary at C4. However, while the regioselectivity of the process was full, the chemical yield of the addition was a function of the nature of both the metal reagent and the system solvent as well. In addition, 2-azetidinone-tethered 1,3-butadienes can easily be transformed into other functionalities via Diels−Alder reaction.

Introduction

The complexity of organic target molecules is constantly increasing, and novel strategies allowing the efficient formation of new carbon−carbon bonds between functionalized moieties are needed. Among the most fundamental and important reactions for constructing carbon−carbon bonds are the allylation and the propargylation/allenylation of aldehydes and ketones (carbonyls) with organometallic reagents.[1,2] In contrast, the analogous reaction involving butadienylmetals has been much less investigated. The use of lithium-,[3] magnesium-,[4] tin-,[5] silicon-,[6] and boron-based[7] reagents has been reported in anhydrous organic solvents. However, 2-(1,3-butadienyl)magnesium chloride has the serious disadvantage of poor regioselectivity, and its lithium counterpart must be prepared indirectly from the corresponding stannnane. The preparation of the others above organometallic derivatives (stannane, silane, and boronate) generally requires tedious protocols, and these reagents are not recommended from an atom economy criterion. Thus, searching for new synthetic equivalents accessible for simple starting materials is of interest. In view of the particular effort devoted to organometallic reactions in aqueous media because of its synthetic advantages as well as its potential as an environmentally benign chemical process,[8] Chan and colleagues have reported the indium-mediated 1,3-butadien-2-ylation of simple aldehydes in aqueous medium.[9] To the best of our knowledge, however, the zinc-promoted 1,3-butadien-2-ylation or the metal-promoted 1,3-butadien-2-ylation using propargylic dimesylates have never been reported. As part of our ongoing project in the synthesis of natural products and derivatives from 2-azetidinones,[10] we decided to pursue eco-friendly approachs to 3-substituted 3-hydroxy-*β*-lactams, because of the importance both as substrates for the "*β*-lactam synthon method" and for studies of biological activity. The 3-substituted 3-hydroxy-*β*-lactam moiety represents an efficient carboxylate mimic,[11] and it is present in several pharmacologically active monobactams such as sulfazecin and related products,[12] and in enzyme inhibitors such as tabtoxin and its analogues.[13]

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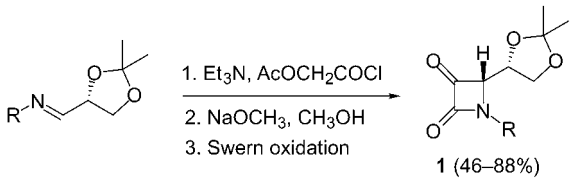
Scheme 1



In addition, these compounds with correct absolute configurations serve as precursors to the corresponding α-hydroxy-*β*-amino acids (isoserines), which are key components of a large number of therapeutically important compounds. As an example, (2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid (norstatine) and (3*R*,4*S*)-4-amino-3-hydroxy-5-methylheptanoic acid (statine) are residues for peptide inhibitors of enzymes, such as renin[14] and HIV-1 protease.[15] Moreover, phenylisoserine analogues are used to synthesize new taxoids.[16] Herein, we wish to report the metal-mediated 1,3-butadien-2-ylation of enantiomerically pure azetidine-2,3-diones **1** in aqueous media using 1,4-dibromo-2-butyne **2** or 1,4-bis(methanesulfonyl)-2-butyne **3**, which resulted in the corresponding 3-butadienyl 3-hydroxy-*β*-lactams.

Results and Discussion

The starting azetidine-2,3-diones **1** were efficiently prepared in optically pure form from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, via Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation, as we previously reported (Scheme 1).[10f] Our aim was set to carry out the key coupling reactions, evaluating the regiochemistry of the connection (e.g., butadienylation vs homoallenylation) and the diastereochemistry (syn vs anti). The interest in an enviromentally benign approach prompted us to seek an aqueous metal-induced 1,3-butadien-2-ylation reaction. To achieve full stereocontrol, we placed a bulky chiral auxiliary at C4 that might be able to control the stereochemistry of the new C3-substituted C3-hydroxy quaternary center. For the purpose of full control of regiochemistry, azetidine-2,3-diones **1** were treated with 1,4-dibromo-2-butyne **2** and a broad variety of metals and reaction conditions in aqueous media. Not unexpectedly, the diastereoselectivity was complete in all cases. However, while the regioselectivity of the process was full, the chemical yield of the addition was a function of the nature of both the metal reagent and the system solvent as well.

Since indium chemistry has captured much recent attention largely due to the discovery that indium can mediate in aqueous media the smooth coupling of allylic halides with aldehydes to give the corresponding homoallylic alcohols,[8] the regio- and diastereoselectivity of the carbon−carbon bond formation were initially investigated through the indium-mediated reaction between the azetidine-2,3-dione (+)-**1a** and 1,4-dibromo-2-butyne in aqueous tetrahydrofuran (1:1) at room temperature. In the event, the 3-(1,3-butadien-2-yl) 3-hydroxy-*β*-lactam (+)-**4a** was obtained in 54% as the only regio- and stereoisomer (Table 1, entry 1). Because water is an economical solvent, we decided to increase the amount of water in the Barbier-type reaction. However, when the reaction was conducted in a THF/H_2O (1:5) mixture, the coupling was not as efficient as before (18% yield). A higher proportion of THF beyond the 1:1 ratio in the solvent did not seem to improve the yield further. It was reported for the Barbier-type allylation of 2-aminoaldehydes in aqueous media that changes in the ionic strength of the solvent can provide modification in the diastereomeric ratio or accelerated the process,[17] and we have described a conversion enhancement for the carbonyl-allenylation reaction in the presence of ammonium chloride.[10d] In contrast, the ionic strength enhancement of the reaction solvent provided by the ammonium chloride was counterproductive for the indium-mediated 1,3-butadien-2-ylation. Thus, moving from THF/H_2O (1:1) to THF/NH_4Cl (aq satd) (1:1) decreased the yield for the indium-promoted reaction between 1,4-dibromo-2-butyne and azetidine-2,3-dione (+)-**1a** (Table 1, entries 1 and 3). The reaction time was increased by 20 (Table 1, entry 4) as the solvent changed from tetrahydrofuran/H_2O (1:1) to a methanol/H_2O (1:1) mixed solvent. No reaction was observed in $THF/NaHCO_3$ (aq satd) (1:1). When the above coupling was promoted by zinc in THF/NH_4Cl (aq satd) (1:5), it gave rise to the optically pure 1,3-butadien-2-yl alcohol (+)-**4a** as a single isomer in 30% yield. The yield fell considerably by performing the zinc-mediated reaction in THF/H_2O (1:1) (Table 1, entry 7). Tin, cadmium, and bismuth failed to produce any desired product when they were used as metal promoters. These results suggest that the metal-promoted carbonyl-1,3-butadien-2-ylation in aqueous media may be quite sensitive to various factors.

Next, we explored 1,4-bis(methanesulfonyl)-2-butyne **3** as a Barbier-type 1,3-butadien-2-ylating reagent, rather than 1,4-dibromo-2-butyne **2**, because the mesylates are superior to the halides for ease of preparation and the stability of propargylic substrates.[18] The bismesylate **3** was then reacted with azetidine-2,3-diones **1**, sodium iodide, and indium in different aqueous media to afford the corresponding (buta-1,3-dien-2-yl)methanol derivatives **4** in moderate yield (up to 42%). In all cases, the same regioselectively was observed, but the conversion was enhanced as the system solvent changed from THF/H_2O (1:1) to THF/NH_4Cl (aq satd) (1:5). No reaction was observed when the indium was supressed by using another metal promoter. Similar results were observed in the metal-mediated reactions of different N-substituted α-keto-lactams **1** with the dibromide **2** or the bismesylate **3** (see Table 1). From a synthetic point of view, the use of 1,4-dibromo-2-butyne is potentially advantageous over the use of 1,4-bis(methanesulfonyl)-2-butyne because a slightly higher yield was obtained. However, it is noteworthy that 1,4-dibromo-2-butyne is a powerful vesicant and lachrymator,[19] and on a multigram-scale the bisme-

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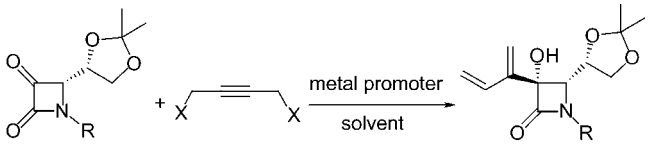
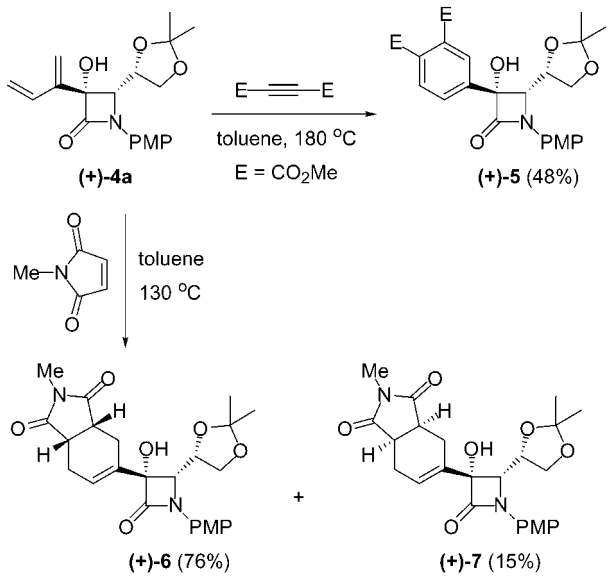
Table 1. Regio- and Stereoselective 1,3-Butadien-2-ylation of Azetidine-2,3-diones 1 in Aqueous Media[a]



entry	ketone	R	X	metal	system solvent	*t* (h)	compd[b]	yield[c] (%)
1	(+)-**1a**	PMP	Br	In	THF/H_2O (1:1)	1	(+)-**4a**	54
2	(+)-**1a**	PMP	Br	In	THF/H_2O (1:5)	1	(+)-**4a**	18
3	(+)-**1a**	PMP	Br	In	THF/NH_4Cl (aq satd) (1:1)	4	(+)-**4a**	19
4	(+)-**1a**	PMP	Br	In	MeOH/H_2O (1:1)	20	(+)-**4a**	26
5	(+)-**1a**	PMP	Br	In	THF/$NaHCO_3$ (aq satd) (1:1)			
6	(+)-**1a**	PMP	Br	Zn	THF/NH_4Cl (aq satd) (1:5)	18	(+)-**4a**	30
7	(+)-**1a**	PMP	Br	Zn	THF/H_2O (1:1)	18	(+)-**4a**	9
8	(+)-**1a**	PMP	MsO	In	THF/NH_4Cl (aq satd) (1:5)	4	(+)-**4a**	42
9	(+)-**1a**	PMP	MsO	In	THF/H_2O (1:1)	5	(+)-**4a**	32
10	(−)-**1b**	2-propenyl	Br	In	THF/H_2O (1:1)	1	(−)-**4b**	62
11	(−)-**1c**	2-propynyl	Br	In	THF/H_2O (1:1)	1	(+)-**4c**	38
12	(−)-**1d**	3-butenyl	Br	In	THF/H_2O (1:1)	1	(+)-**4d**	45
13	(−)-**1b**	2-propenyl	MsO	In	THF/NH_4Cl (aq satd) (1:5)	4	(−)-**4b**	33
14	(−)-**1c**	2-propynyl	MsO	In	THF/NH_4Cl (aq satd) (1:5)	4	(+)-**4c**	37
15	(−)-**1d**	3-butenyl	MsO	In	THF/NH_4Cl (aq satd) (1:5)	4	(+)-**4d**	34

[a] All reactions were carried out on 1 mmol scale. PMP = 4-$MeOC_6H_4$. [b] Obtained as single regio- and stereoisomers, to judge by the ^1H NMR spectra of the crude reaction mixtures before purification. [c] Yield of pure, isolated product with correct analytical and spectral data.

Scheme 2



sylate protocol may be practically useful. Nonetheless, there remains much room for improvement in respect to yield.

The stereochemistry at the C3-heterosubstituted quaternary center in compounds **4** was established by qualitative homonuclear NOE difference spectra performed on 3-hydroxy β-lactams **4.** The facial selectivity of these addition reactions may be controlled by the bulky chiral auxiliary at C-4 in which one face of the ketone is blocked, thus the organometallic reagent being delivered preferentially to the less hindered face.

2-Functionalized-1,3-butadienes are quite useful building blocks in organic synthesis because the butadiene moiety can easily be transformed into other functionalities, specially via Diels−Alder reaction.[20] The usefulness of the 3-butadienyl 3-hydroxy-β-lactams **4** becomes much higher by assuming that the (buta-1,3-dien-2-yl)methanol moiety is a placeholder for further conversions. As shown in Scheme 2, the Diels−Alder reaction with concomitant aromatization proceeded by treating the compound (+)-**4a** with dimethyl acetylenedicarboxylate, affording cycloadduct (+)-**5**. Next, we studied the reactivity of 2-azetidinone-tethered diene (+)-**4a** with a cyclic dienophile. Intermolecular Diels−Alder cycloaddition of diene (+)-**4a** with *N*-methylmaleimide proceeded to give products (+)-**6** and (+)-**7** in a 5:1 ratio, which were separated by column chromatography (Scheme 2).[21]

Conclusions

In conclusion, we have achieved a highly regio- and diastereoselective metal-mediated 1,3-butadien-2-ylation of azetidine-2,3-diones in aqueous media, which afforded the potentially bioactive 3-substituted 3-hydroxy-β-lactam moiety. In addition, the present study provides the first insight into the manner in which the carbonyl group and 1,4-bis(methanesulfonyl)-2-butyne undergo metal-mediated coupling. The simple reaction protocol, in combination with options for further transformations of the resulting adducts, makes this process more useful.

Experimental Section

General Methods. General experimental data and procedures have been previously reported.[10a] NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Specific rotation $[\alpha]_D$ is given in deg per dm at 20 °C, and the concentration (*c*) is expressed in g per 100

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mL. Flash column chromatography was performed on silica gel (230−400 mesh). All commercially available compounds were used without further purification.

General Procedure for the Indium-Promoted Reaction between 1,4-Dibromo-2-butyne and Azetidine-2,3-diones in Aqueous Medium. 1,4-Dibromo-2-butyne **2** (2.0 mmol) was added to a well-stirred suspension of the corresponding α-keto lactam **1** (1.0 mmol) and indium powder (1.99 mmol) in THF/H_2O (1:1, 5 mL) at 0 °C. After 1 h at room temperature, saturated aqueous ammonium chloride (2 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature before being extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexane mixtures gave analytically pure compounds **4**. Spectroscopic and analytical data for some representative forms of **4** follow.[22]

(3*R*,4*S*)-3-(1,3-Butadien-2-yl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(*p*-methoxyphenyl)-2-azetidinone, (+)-4a. From 43.5 mg (0.15 mmol) of azetidine-2,3-dione (+)-**1a** was obtained 30.9 mg (54%) of compound (+)-**4a** as a colorless oil. $[\alpha]_D = +341.9$ (*c* 0.8, $CHCl_3$). ^{1}H NMR: δ 1.35 and 1.46 (s, each 3H), 3.72 (m, 1H), 3.73 (s, 3H), 4.12 (d, 1H, $J = 6.8$ Hz), 4.29 (dd, 1H, $J = 8.8$, 6.8 Hz), 4.53 (q, 1H, $J = 6.8$ Hz), 4.80 (brs, 1H), 5.17 (dd, 1H, $J = 11.1$, 1.1 Hz), 5.37 and 5.46 (s, each 1H), 5.48 (dd, 1H, $J = 17.3$, 1.2 Hz), 6.25 (ddd, 1H, $J = 17.6$, 11.1, 0.8 Hz), 6.87 and 7.61 (d, each 2H, $J = 9.3$ Hz). ^{13}C NMR: δ 166.9, 156.8, 143.3, 133.5, 130.6, 120.1, 117.4, 115.5, 114.1, 109.8, 85.4, 66.5, 66.2, 65.8, 55.4, 26.5, 25.1. IR ($CHCl_3$, cm^{-1}): ν 3340, 1742. MS (CI) *m*/*z*: 346 ($M^+ + 1$, 100), 345 (M^+, 17). Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.14; H, 6.66; N, 4.01.

(3*R*,4*S*)-3-(1,3-Butadien-2-yl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(2-propenyl)-2-azetidinone, (−)-4b. From 48 mg (0.213 mmol) of azetidine-2,3-dione (−)-**1b** was obtained 37 mg (62%) of compound (−)-**4b** as a colorless oil. $[\alpha]_D = -14.7$ (*c* 0.7, $CHCl_3$). ^{1}H NMR: δ 1.28 and 1.37 (s, each 3H), 3.60 (d, 1H, $J = 6.1$ Hz), 3.72 (ddt, 1H, $J = 15.1$, 7.3, 1.0 Hz), 3.76 (dd, 1H, $J = 8.9$, 5.3 Hz), 4.20 (dd, 1H, $J = 8.9$, 7.0 Hz), 4.29 (ddt, 1H, $J = 15.4$, 4.6, 1.7 Hz), 4.44 (td, 1H, $J = 6.6$, 5.4 Hz), 5.24 (m, 3H), 5.33 and 5.41 (s, each 1H), 5.54 (dd, 1H, $J = 17.3$, 1.5 Hz), 5.76 (m, 1H), 6.26 (ddd, 1H, $J = 17.3$, 11.0, 0.9 Hz). ^{13}C NMR: δ 169.1, 143.5, 133.8, 131.2, 118.8, 117.3, 115.1, 109.9, 86.2, 75.6, 66.5, 65.1, 43.4, 26.5, 24.9. IR ($CHCl_3$, cm^{-1}): ν 3342, 1744. MS (CI) *m*/*z*: 280 ($M^+ + 1$, 100), 279 (M^+, 21). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.58; H, 7.56; N, 5.00.

General Procedure for the Indium-Promoted Reaction between 1,4-Bis(methanesulfonyl)-2-butyne and Azetidine-2,3-diones in an Aqueous Medium Containing NH_4Cl. 1,4-Bis(methanesulfonyl)-2-butyne **3** (3.0 mmol) was added to a well-stirred suspension of the corresponding α-keto-lactam **1** (1.0 mmol), sodium iodide (6.0 mmol), and indium powder (1.99 mmol) in THF/NH_4Cl (aq satd) (1:5, 5 mL) at 0 °C. After 4 h at room temperature, the mixture was extracted with ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **4**.

(3*R*,4*S*)-3-(1,3-Butadien-2-yl)-1-(3-butenyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-2-azetidinone, (+)-4d. From 54 mg (0.226 mmol) of azetidine-2,3-dione (−)-**1d** was obtained 22 mg (34%) of compound (+)-**4d** as a colorless oil. $[\alpha]_D = +1.1$ (*c* 0.8, $CHCl_3$). ^{1}H NMR: δ 1.36 and 1.45 (s, each 3H), 2.37 (m, 2H), 3.27 (m, 1H), 3.57 (d, 1H, $J = 7.3$ Hz), 3.67 (m, 2H), 4.22 (dd, 1H, $J = 8.7$, 6.7 Hz), 4.18 (s, 1H), 4.41 (dt, 1H, $J = 7.0$, 5.8 Hz), 5.08 (m, 2H), 5.19 (dd, 1H, $J = 11.0$, 1.5 Hz), 5.33 and 5.37 (s, each 1H), 5.54 (dd, 1H, $J = 17.6$, 1.6 Hz), 5.77 (m, 1H), 6.25 (ddd, 1H, $J = 17.3$, 11.0, 0.9 Hz). ^{13}C NMR: δ 169.1, 143.6, 134.8, 133.7, 117.3, 117.1, 114.8, 109.7, 85.8, 76.1, 66.6, 65.6, 40.4, 31.6, 26.6, 25.0. IR ($CHCl_3$, cm^{-1}): ν 3343, 1745. MS (CI) *m*/*z*: 294 ($M^+ + 1$, 100), 293 (M^+, 19). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.59; H, 7.88; N, 4.75.

Procedure for the Preparation of Adduct (+)-5. To a solution of the diene (+)-**4a** (52 mg, 0.151 mmol) and hydroquinone (cat.) in toluene (10 mL) was added dimethyl acetylenedicarboxylate (26 mg, 0.181 mmol). The resulting solution was heated in a sealed tube at 180 °C for 22 h. The reaction mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure. Chromatography of the residue eluting with dichloromethane/ethyl acetate (9:1) gave 36 mg (48%) of analytically pure adduct (+)-**5** as a colorless oil. $[\alpha]_D = +54.1$ (*c* 1.2, $CHCl_3$). ^{1}H NMR: δ 1.37 and 1.43 (s, each 3H), 3.82 (s, 3H), 3.83 (m, 1H), 3.90 and 3.91 (s, each 3H), 4.17 (d, 1H, $J = 6.3$ Hz), 4.31 (dd, 1H, $J = 8.8$, 6.8 Hz), 4.56 (q, 1H, $J = 6.6$ Hz), 6.91 (d, 2H, $J = 9.0$ Hz), 7.53 (dd, 1H, $J = 8.2$, 1.8 Hz), 7.63 (d, 2H, $J = 9.0$ Hz), 7.71 (d, 2H, $J = 8.0$ Hz), 7.76 (d, 1H, $J = 1.9$ Hz). ^{13}C NMR: δ 167.3, 157.2, 141.8, 133.0, 131.7, 129.7, 127.5, 125.4, 120.5, 114.3, 110.2, 85.0, 76.0, 69.3, 66.5, 55.5, 26.4, 25.2. IR ($CHCl_3$, cm^{-1}): ν 3343, 1725, 1745. MS (EI), *m*/*z*: 486 ($M^+ + 1$, 38), 485 (M^+, 100). Anal. Calcd for $C_{25}H_{27}NO_9$: C, 61.85; H, 5.61; N, 2.89. Found: C, 61.77; H, 5.63; N, 2.90.

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Supporting Information Available: Spectroscopic and analytical data for compounds **1a**−**d**, **3**, (+)-**4d**, (+)-**6**, and (+)-**7**, as well as general experimental procedures for compounds **1a**−**d**, **3**, **4a**−**d**, (+)-**6**, and (+)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.