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Stereoselective Formal Total Synthesis of (+)-Methynolide

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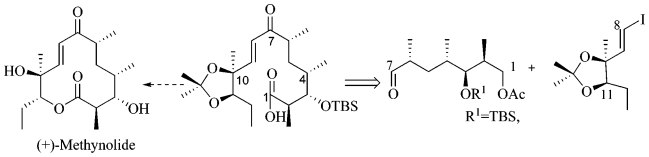

A highly stereoselective and convergent formal total synthesis of (+)-methynolide is described. The salient features of this synthesis have been the construction of the C1−C7 and C8−C11fragments via a desymmetrization approach, Sharpless asymmetric epoxidation of an allyl alcohol, respectively, and linkage of both the fragments by Nozaki−Hiyama−Kishi reaction.

Stereocontrolled synthesis of macrolide antibiotics is one of the most attractive areas in current synthetic organic chemistry, and various new synthetic methodologies have been developed en route to the synthesis of such complex molecules.[1] The methymycin family of antibiotics comprises three 12-membered macrolides isolated from *Streptomyces* species methymycin,[2] neomethymycin, and 10-deoxymethymycin[3] that display antibiotic activity against Gram-positive bacteria. The structures of all of these three macrolides were confirmed by the chemical degradation studies, spectroscopic analysis, and finally by their total synthesis.[4]

Efforts toward the total synthesis of methynolide mainly centered on the construction of Prelog Djerassi lactone unit[5] **7**, a key degradation product retaining the original four chiral centers present in the C1 to C7 segment of the methynolide skeleton. Since the first total synthesis of methynolide by Masamune, several reports on the total synthesis[6] or the corresponding seco acid derivative of methynolide[7] (Figure 1) have been published. In continuation of our ongoing research on the synthesis of polyketide natural products using the desymmetrization strategy, we report herein the formal and convergent total synthesis of (+)-methynolide **1**.

The retrosynthetic analysis of **1** is depicted in Figure 2. The key intermediate **3** led us to a convergent approach (Figure 2). Methynolide can be derived from the intermediate **3**, which in turn can be obtained by coupling of **4** (C1−C7) and **5** (C8−C11) fragments. Compound **4** can be derived from lactone **7** via triol **6**, and vinyl iodide **5** can be obtained from the α,β-unsaturated ester **9**.

Synthesis of the fragment **4** (Scheme 1) began with the reductive cleavage of the bicyclic lactone **7**, the synthesis of which was discussed earlier by the desymmetrization of a bicyclic olefin.[8] Thus treatment of **7** with lithium aluminum hydride (LAH) in THF at rt furnished triol **10** in 90% yield. The transformation of **10** into **4** warranted the configuration of the hydroxyl group at the C3 position to be inverted and the C5 oxygen to be deoxygenated. Accordingly, the triol **10** was chemoselectively protected as disilyl ether[9] **11** using TBSCl and imidazole in dichloromethane. Attempted inversion of the secondary hydroxyl group in **11** using the Mitsunobu protocol[10]met with failure. Alternatively, it was achieved by oxidation followed by reduction of **11**. Thus oxidation of **11** with Dess-Martin periodinane[11] yielded ketone **12** in 92% overall yield from **10**. Subsequently, reduction of **12** with DIBAL-H afforded exclusively alcohol **13**, a result of 1,3-*syn* reduction[12] with an overall inversion of the C3 hydroxyl group. Protection of the hydroxyl group as its MOM ether[13] **14** using MOM−Cl and diisopropylethyl amine and treatment of **14** with DDQ[14] in a biphasic mixture of dichloromethane and water (10:1) yielded a secondary alcohol **15**. Xanthate ester **16** was obtained on treatment of

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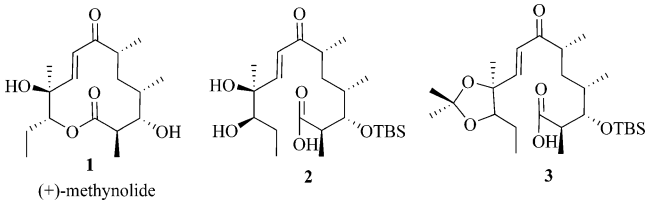

FIGURE 1. Structures of methynolide (**1**), seco acid (**2**), and an advanced intermediate (**3**).

15 with NaH, carbon disulfide, and methyl iodide. Deoxygenation of xanthate ester[15] using tri-*n*-butyl tin hydride in the presence of a catalytic amount of AIBN as a radical initiator yielded **17** in 85% overall yield over three steps.

The deoxygenated product **17** on treatment with 6 N HCl in wet THF afforded the triol **6**. 1,3-Diol system of triol **6** was protected as its corresponding benzylidene acetal **18** with dimethyl acetal of *p*-methoxy benzaldehyde[16] in the presence of a catalytic amount of CSA in dichloromethane. The primary hydroxyl group was subsequently protected as silyl ether **19** using TBS−Cl and imidazole in an overall yield of 83% over three steps. The benzylidene acetal was regioselectively reduced[17] using DIBAL-H in dichloromethane at −15 °C to yield a free primary alcohol **20**, which was protected as its acetate **21** in 90% overall yield. Deprotection of *p*-methoxybenzyl ether using DDQ in a biphasic mixture of dichloromethane and water yielded alcohol, which was protected as corresponding silyl ether **22** using TBDMSOTf[18] and 2,6-lutidine in 83% overall yield for two steps. The primary silyl group in **22** was chemoselectively deprotected using PPTS[19] to afford the alcohol **23** in 95% yield. The primary hydroxyl group of **23** was subjected to oxidation with Dess-Martin periodinane to yield the fragment **4** in 90% yield.

Synthesis of fragment **5** (Scheme 2) began with the Wittig reaction of ethyl-2-(triphenylphosphoranylidene)propanoate[20] with propanal to yield an α,*β*-unsaturated ester **9** with exclusively *trans*-configuration in 93% yield. The ester **9** was subjected to alane reduction[21] to yield a *trans* allylic alcohol **24** in 90% yield. The allylic alcohol **24** upon Sharpless asymmetric epoxidation[22,23]—using D-(−)-DIPT afforded the corresponding epoxide **8** in 90% yield in 94% ee. The hydroxyl group of **8** was converted into its corresponding benzyl ether **25** using NaH, BnBr, and a catalytic amount of TBAI in THF. The latter subsequently on treatment with anhydrous acetone in the presence of BF_3-Et_2O[23] at 0 °C furnished the acetonide **26** in 90% overall yield for the last two steps. Debenzylation under Birch conditions[24] with liquid ammonia and lithium metal afforded the primary alcohol **27**, which was oxidized using Dess-Martin periodinane to yield the aldehyde **28**.

The aldehyde was treated with carbon tetrabromide and triphenylphosphine (Corey−Fuch's protocol)[25] to obtain the corresponding dibromoolefin **29** in an overall yield of 65% over three steps. The dibromoolefin **29** upon treatment with 6.0 equiv of ethyl magnesium bromide yielded alkyne **30** in 90% yield. Hydrostannation of **30** with tri-*n*-butyl tin hydride in the presence of a catalytic amount of radical initiator AIBN in benzene under reflux conditions afforded exclusively *trans*-vinylstannane **31**, treatment of which with 2.0 equiv of iodine in dichloromethane furnished *trans*-vinyl iodide **5** in 93% overall yield for two steps. Alternatively, the *trans*-iodoolefin **5** can also be obtained from aldehyde **28** by Takai's olefination as mentioned in previous reports.[7d] The *trans*-configuration was confirmed by the coupling constant of the olefinic protons (14.3 Hz). The optical rotation of compound **5**, $[\alpha]^{25}_D = +2.4$ (*c* 1.85, $CHCl_3$), was in agreement with a literature report.[7d]

Fragments **4** and **5** were then coupled following Nozaki−Hiyama−Kishi protocol[26] (Scheme 3). The aldehyde **4** was added to a suspension of $CrCl_2$ and $NiCl_2$ in anhydrous DMF at rt, followed by the addition of the iodo compound **5** predissolved in DMF, to afford the coupled product **32** in the form of a diastereomeric mixture in 65% yield. Hydrolysis of **32** with a catalytic amount of K_2CO_3 in methanol afforded diol **33** in quantitative yield, which on oxidation with Dess-Martin periodinane afforded the ketoaldehyde which was further oxidized to acid **3** using $NaClO_2$[27] in the presence of 2-methyl-2-butene in a mixture of *tert*-butanol and water at 0 °C in 90% yield.

The optical rotation and the spectral data of the acid **3** were in accordance with literature.[7b] The synthesis of (+)-methynolide in two steps from the acid intermediate **3** has been reported by Masamune.[4b] Thus, a formal total synthesis of (+)-methynolide has been accomplished.

In conclusion, we have completed the formal total synthesis of (+)-methynolide in a convergent manner employing the Nozaki−Hiyama−Kishi coupling for the union of two fragments **4** and **5**, a desymmetrization approach for highly stereoselective synthesis of the C1−C7 fragment **4**, and Sharpless asymmetric epoxidation of an allyl alcohol as a key transformation for the synthesis of C8−C11 fragment **5**.

Experimental Section

(*E*,2*S*,3*S*,4*S*,6*R*)-9-((4*S*)-5-Ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)-3-hydroxy-7-*O*-(*tert*-butyldimethylsilyl)-2,4,6-trimethylnon-8-enyl acetate, 32. In a 25 mL clean and dry two-neck round-bottomed flask equipped with a magnetic bar and septum was weighed anhydrous $CrCl_2$ (146 mg, 1.18 mmol) and a trace of anhydrous $NiCl_2$. To it was added 2.0 mL of anhydrous DMF, and the suspension was stirred at rt for 10 min. Aldehyde **4** (104 mg, 0.297 mmol) predissolved in 1.0 mL of dry DMF was added to the reaction mixture and stirred at rt for 10 min. To the reaction mixture then was added the iodoolefin **5** (176 mg, 0.594 mmol) in anhydrous DMF (1 mL). The reaction was stirred at rt for 20 h. After the completion of the reaction, the reaction mixture was diluted with

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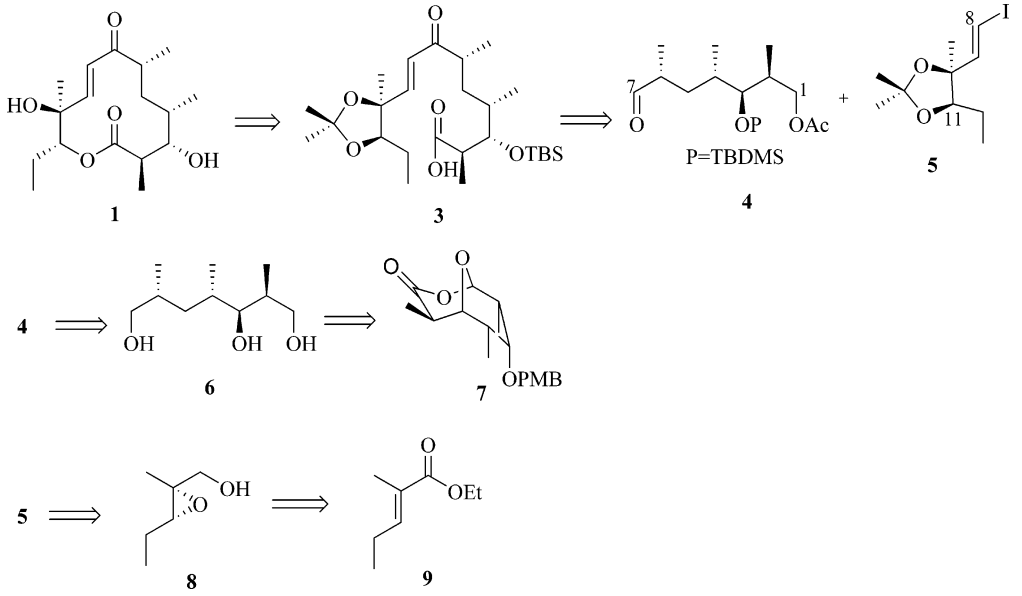
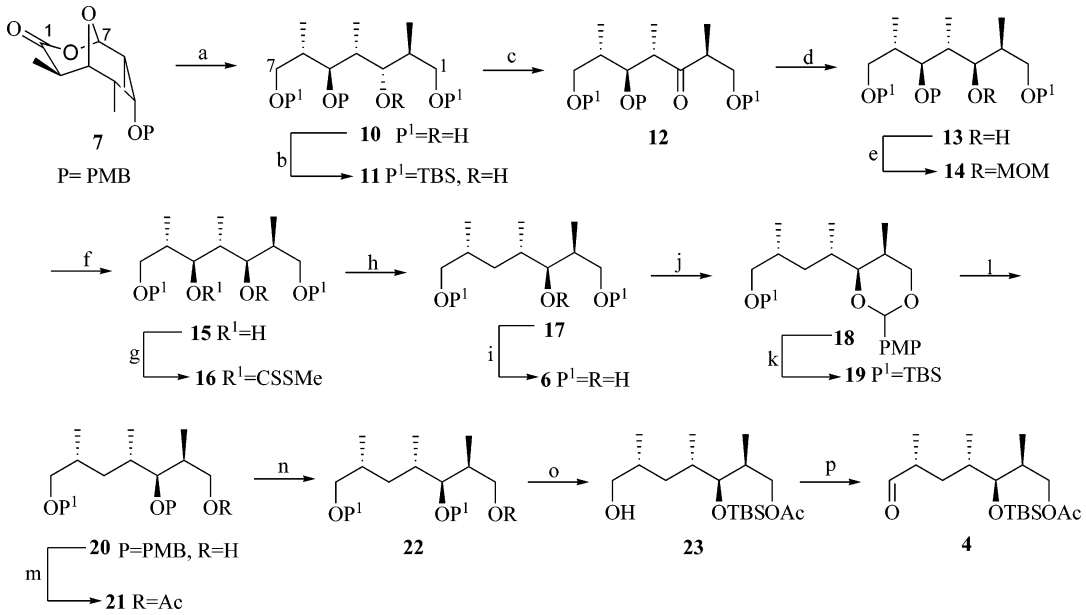


FIGURE 2. Retrosynthetic analysis of an advanced intermediate **3**.

SCHEME 1. Synthesis of C1−C7 Fragment, 4[a]

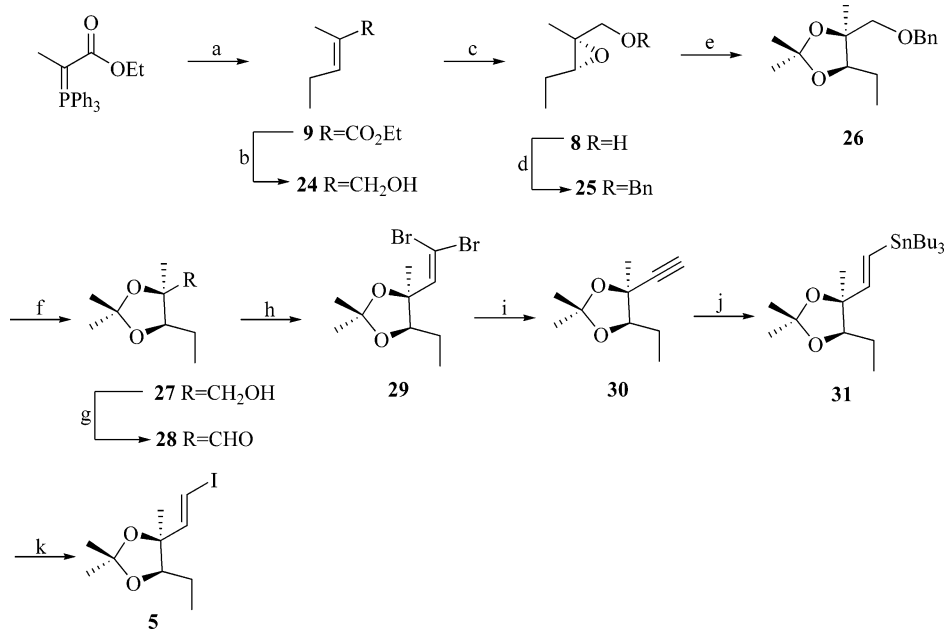


[a] Reagents and conditions: (a) $LiAlH_4$, ether, 0 °C to rt, 90%; (b) TBDMSCl, imidazole, CH_2Cl_2, 0 °C; (c) Dess-Martin, CH_2Cl_2, 95% from **10**; (d) DIBAL-H, CH_2Cl_2, −78 °C; (e) MOM−Cl, DIPEA, CH_2Cl_2, 0 °C, 90% from **12**; (f) DDQ, CH_2Cl_2/H_2O; (g) NaH, CS_2, MeI, THF, 0 °C; (h) $(^nBu)_3SnH$, cat. AIBN, benzene, reflux, 85% from **14**; (i) 6 N HCl/THF; (j) $(MeO)_2CH(C_6H_4)OMe$, cat. CSA; (k) TBDMSCl, imidazole, CH_2Cl_2, 83% from **17**; (l) DIBAL-H, CH_2Cl_2, 0 °C; (m) Ac_2O, py, DMAP, CH_2Cl_2, 90% from **19**; (n) (i) DDQ, CH_2Cl_2/H_2O, (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 83% over two steps; (o) PPTS, MeOH, rt, 95%; (p) Dess-Martin, CH_2Cl_2, 90%.

ether and quenched with an aqueous solution of NH_4Cl. The product was extracted with ether twice. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford a crude product. The product was then purified on silica gel column using 15% AcOEt/petroleum ether (v/v) as eluent to furnish the pure product **32** as a mixture of epimers (152 mg, 65% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62 (m, 2H), 4.05 (m, 1H), 3.83 (m, 2H), 3.65 (m, 2H), 2.03 (s, 3H), 1.98 (m, 1H), 1.79 (m, 2H), 1.57 (m, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.29 (m, 7H), 1.00 (d, J = 7.6 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.943 (d, J = 6.8 Hz, 3H), 0.89 (m, 9H), 0.04 (d, 6H); HRMS (ES) m/z ($[M + Na]^+$ 537.3609; calcd for $C_{28}H_{54}O_6NaSi$ 537.3587).

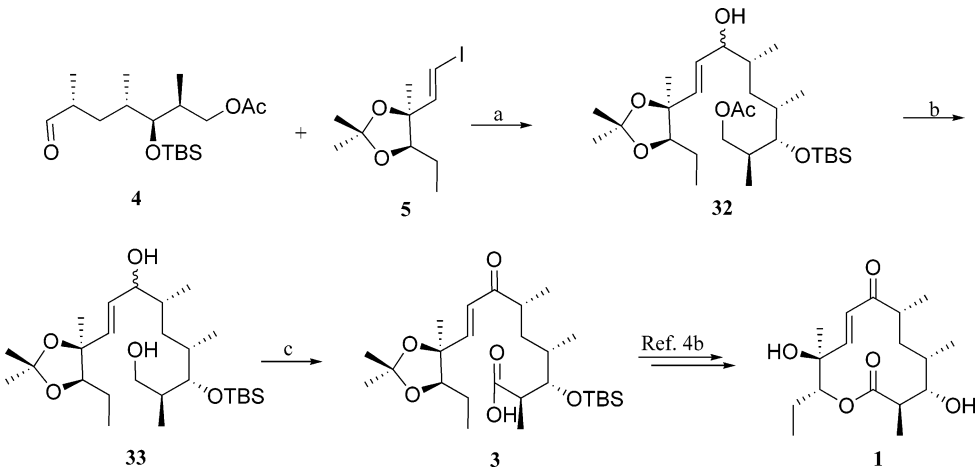
(*E*,2*R*,3*S*,4*S*,6*R*)-9-((4*S*)-5-Ethyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)-3-*O*-(*tert*-butyldimethylsilyl)-2,4,6-trimethyl-7-oxonon-8-enoic acid, 3. To a solution of the diol **33** (115 mg, 0.24 mmol) in dichloromethane in a 25 mL round-bottomed flask equipped with a magnetic bar and nitrogen inlet was added Dess-Martin periodinane reagent (248 mg, 0.58 mmol) at 0 °C, and the reaction mixture was stirred at rt. After the completion of the reaction, petroleum ether (10 mL) was added. The precipitate formed was filtered and the filtrate comprising the ketoaldehyde was concentrated, and the same was used in the next step with out purification. To a solution of ketoaldehyde in a mixture of solvents, *tert*-butanol and water in 3:1 (volume) ratio, at 0 °C was added NaH_2PO_4 (110 mg, 0.705

SCHEME 2. Synthesis of C_8-C_{11} Fragment, 5[a]



[a] Reagents and conditions: (a) propanaldehyde, CH_2Cl_2, rt, 93%; (b) $LiAlH_4$, $AlCl_3$, ether, −10 °C to rt, 90%; (c) D-(−)-DIPT, $Ti(O^iPr)_4$, TBHP, 4 Å MS, CH_2Cl_2, −30 °C, 92%; (d) NaH, BnBr, THF, 0 °C to rt; (e) BF_3-Et_2O, acetone, 0 °C, 90% from **8**; (f) Li/liquid NH_3, THF; (g) Dess-Martin, CH_2Cl_2; (h) CBr_4, PPh_3, CH_2Cl_2, −15 °C, 65% from **26**; (i) EtMgBr, THF, 0 °C to rt, 90%; (j) $(^nBu)_3SnH$, cat. AIBN, C_6H_6, reflux; (k) I_2, CH_2Cl_2, rt, 93% from **29**.

SCHEME 3. Coupling of Fragments 4 and 5 and Completion of Formal Synthesis[a]



[a] Reagents and conditions: (a) $CrCl_2/NiCl_2$, DMF, rt, 65%; (b) cat. K_2CO_3, MeOH, rt, quantitative; (c) (i) Dess-Martin periodinane, CH_2Cl_2, (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (3:1), 0 °C, 90% over two steps.

mmol) followed by 2-methyl-2-butene (230 μL, 0.23 mmol) and stirred for 5 min. $NaClO_2$ (63 mg, 0.705 mmol) was added, and the reaction mixture was stirred at 0 °C. After the completion of the reaction, the solvent mixture was evaporated under reduced pressure and the residue was diluted with AcOEt. The organic layer was washed once with brine and dried over Na_2SO_4 and concentrated to yield a residue which on chromatography (petroleum ether/AcOEt 3:1) afforded the stereochemically pure compound **3** in good yield (78 mg, 70% yield): $[\alpha]^{25}_D = +9.2$ (*c* 0.35, $CHCl_3$), (lit. $[\alpha]^{25}_D = +8.6$ (*c* 0.39, $CHCl_3$)); IR (KBr) 3450, 1720, 1675, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, $J = 15.5$ Hz, 1H), 6.46 (d, $J = 15.5$ Hz, 1H), 3.84−3.80 (m, 2H), 2.79 (ddq, $J = 4.8$, 10, 7 Hz, 1H), 2.63 (dq, $J = J' = 7$ Hz, 1H), 1.88 (ddd, $J = 3.8$, 10, 14 Hz, 1H), 1.59 (br m, 2H), 1.53−1.43 (m, 8H), 1.42 (s, 3H), 1.18 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 6.6$ Hz, 3H), 1.02 (t, $J = 7.3$ Hz, 3H), 0.91 (m, 12H), 0.07 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147, 126, 108, 86.1, 86.07, 82.2, 76.7, 43, 36, 35, 30, 28, 27.9, 26.4, 26, 24.6, 23.2, 18.3, 17.9, 16.4, 11.3, −4.0, −4.2; HRMS (ES) *m/z* ($[M+ Na]^+$ 507.3114; calcd for $C_{26}H_{48}O_6NaSi$ 507.3117).

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Supporting Information Available: Detailed experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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