Registry No. 1, 5815-08-7; 2, 39654-83-6; 3, 41969-71-5; 4, 935-72-8; 5, 41969-73-7; 6a, 86492-07-1; 6b, 86492-08-2; 7a, 86492-10-6; 7b, 87282-76-6; 10, 2044-64-6; 11, 87282-77-7; 12, 87282-78-8; diethyl succinate, 123-25-1.

Novel Synthetic Route to the Key Intermediate for Hirsutic Acid

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Recently we reported the first asymmetric total synthesis of hirsutic acid (1, Chart I), with high stereo- and regiochemical control.[2] In this paper we describe another synthetic route to the key synthetic intermediate **2**, which involves the chelation-controlled methylation from the sterically more crowded face of the molecule.

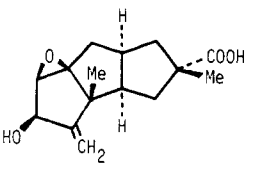
In our previous synthesis,[2] the key intermediate **2** was prepared stereospecifically by using the Simmons–Smith reaction as the key step. Alternatively, we made a search for another stereocontrolled route to **2**. It is generally known that the alkylation of the enolates generated from the compounds such as **3** proceeds predominantly at the convex face of the *cis*-bicyclo[3.3.0]octane skeleton. In fact, the methylation of the lithium enolate derived from **4** afforded a mixture of **8** and **9** in a ratio of 1.7:1 (LDA, THF, MeI), suggesting that it is unlikely to accomplish an alternative and efficient synthesis of **2** by using this methodology. However, it was assumed that, with the ester **5** carrying the MEM ether in the endo configuration, the resulting lithium enolate would preferentially exist in some rigid chelate, fixing the lithium ion on the endo side. Furthermore, we anticipated that the unshared electrons of iodine would coordinate to the lithium cation,[3] allowing an approach of methyl iodide at the concave face.

In order to test our assumption, the ester **5** was prepared as follows. Successive treatment of the MEM ether **10**[4] with (1) NBS in aqueous Me_2SO, (2) tributyltin hydride in benzene containing a catalytic amount of AIBN, and (3) PCC in methylene chloride afforded the ketone (**11**) in 50% overall yield with high regiochemical control.[5] The ketone **11** was reacted with (methoxymethylene)triphenylphosphorane to give the enol ether **12** in 85% yield. Hydrolysis of **12** with AcOH–H_2O–THF (3:1:1) produced the aldehyde **13**, which was then successively treated with Jones reagent and ethereal diazomethane to afford the ester **5** as a mixture of the stereoisomers **5a**/**5b** (ca. 5:1) in 68% overall yield. The stereochemistry of both **5a** and **5b** was tentatively assigned on the basis of the observation that treatment of either **5a** or **5b** with LDA in THF, followed by the kinetic protonation, afforded the ester **5b** as the major product in a ratio of ca. 5:1 **5b**/**5a**.

In the first place, the alkylation reaction of **5** was carried out in THF with LDA as a base and methyl iodide as an alkylating agent. As was expected, it was observed that the methyl ester **14** was formed as a major product though in a low stereoselectivity (**14**/**15**, 1.2:1). The product ratio was determined from the ^1H NMR spectrum of a mixture of the products, which displayed two singlets at δ 1.30 (**14**) and 1.20 (**15**). Being encouraged by these results, we examined a variety of reaction conditions in order to improve the stereoselectivity. At first, solvent effects were studied in detail, showing that the alkylation reaction in ether provides **14** with the highest stereoselectivity (**14**/**15**, 2.3:1; 87% yield). The results are summarized in Table I.

Use of other protecting groups of the hydroxy functionality did not improve the stereoselectivity.[6] For ex-

Chart I



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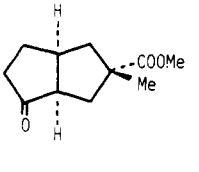

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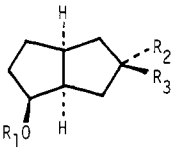
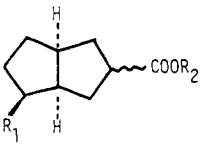
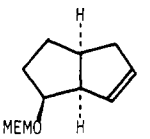


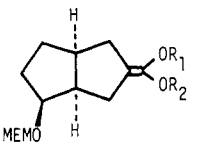


5a: R_1=MEM, R_2=COOMe, R_3=H
5b: R_1=MEM, R_2=H, R_3=COOMe
8: R_1=CH_2Ph, R_2=Me, R_3=COOMe
9: R_1=CH_2Ph, R_2=COOMe, R_3=Me
11: R_1=MEM, R_2-R_3=O
12: R_1=MEM, R_2-R_3=CHOMe
13: R_1=MEM, R_2=CHO, R_3=H
14: R_1=MEM, R_2=COOMe, R_3=Me
15: R_1=MEM, R_2=Me, R_3=COOMe
16: R_1=MOM, R_2=COOMe, R_3=Me
17: R_1=MOM, R_2=Me, R_3=COOMe
20: R_1=MEM, R_2=COO*i*-Pr, R_3=Me
21: R_1=MEM, R_2=Me, R_3=COO*i*-Pr
22: R_1=H, R_2=COOMe, R_3=Me

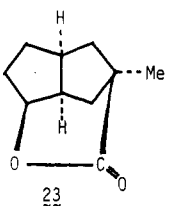
3: R_1=H, R_2=Me
4: R_1=OCH_2Ph, R_2=Me
5: R_1=OMEM, R_2=Me
6: R_1=OMOM, R_2=Me
7: R_1=OH, R_2=Me
19: R_1=OMEM, R_2=*i*-Pr



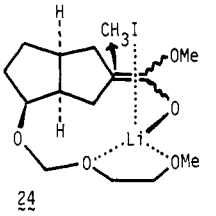
10



18a: R_1=Me, R_2=Li
18b: R_1=Li, R_2=Me



23



24

Table I. Methylation Reaction of the Ester 5 in Various Solvents[a]

solvent	product ratio 14	15
THF	1.2	1.0
ether	2.3	1.0
DME	2.0	1.0
MeOMe	1.4	1.0
$(MeO)_2CH_2$	1.4	1.0

[a] All reactions were carried out by using LDA as a base and me thyl iodide as an alkylating agent.

(1) Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan.
(2) Shibasaki, M.; Yamazaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1982**, 5311.
(3) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.
(4) Prepared in large quantities by starting with 1,3-cyclooctadiene in three steps. See: Crandall, J. K.; Chang, L.-H. *J. Org. Chem.* **1967**, *32*, 532.
(5) Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Chem. Lett.* **1981**, 1245.
(6) The hydroxy ester **7** was also employed for the methylation reaction in order to examine the effects of the lithium alkoxide moiety on the stereoselectivity of the alkylation reaction. However, in this case the lactone **23** was formed exclusively.

0022-3263/83/1948-4402$01.50/0

ample, in the case of **6**, the alkylation reaction in ether provided the isomeric methyl esters only in a ratio of 1.5:1 **16**/**17**. Use of other metal enolates such as the zinc enolate afforded the isomeric methyl esters only in modest yields with the lower stereoselectivities.

In order to clarify the effects of the configuration of the methoxycarbonyl group in **5**, which might have the influence on the ester enolate configuration,[7] the stereochemically pure ester **5a** was subjected to the alkylation reaction under the conditions described above (LDA, ether) to give a slightly higher stereoselectivity than in the case of **5** (**14**/**15**, 2.4:1). While the endo ester **5b** afforded the somewhat lower stereoselectivity (**14**/**15**, 1.5:1). These results suggested that the exo ester **5a** might lead to the ester enolate **18a** more preferentially than to the stereoisomer **18b**, being converted to the methyl ester **14** more stereoselectively than in the case of the endo ester **5b**.[8]

Dimethyl sulfate was next employed as a methylating agent in place of methyl iodide, giving a less satisfactory result (**14**/**15**, 1.4:1). The other esters such as the isopropyl ester **19** were also subjected to the methylation reaction. In this reaction, it was likely that the more crowded ester moiety would prevent more efficiently an approach of methyl iodide from the convex face of the molecule, providing the desired product **20** more stereoselectively. However, also in this case, the lower stereoselectivity (**21**/**20**, 1.1:1) was observed.

Although the stereoselectivity of the present methylation reaction (**14**/**15**, 2.4–2.3:1) is not satisfactory, the results obtained above are worthy of note.

A mixture of the stereoisomers **14**/**15** (2.3:1), not separable easily at this stage, was treated with 1% sulfuric acid in acetone–water (7:1) to provide the alcohol **22** and the lactone **23** in a ratio of ca. 2.3:1 (80% yield). The alcohol **22**, easily separated from **23**, was oxidized with PCC to afford the ketone **2** in nearly quantitative yield, which was spectroscopically superimposable with an authentic material.[2]

Thus, an alternative and stereoselective route to the key intermediate **2** for hirsutic acid (**1**) employing the chelation-controlled alkylation probably via a transition state such as **24** was realized.

Experimental Section

IR spectra were measured on a Hitachi 215 grating infrared spectrometer. ^{1}H NMR spectra were recorded with a Varian EM360A NMR spectrometer or a Varian XL-100-12 NMR spectrometer ($CDCl_3$ solutions) with tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained from a JEOL JMS-D300 mass spectrometer and high-resolution mass spectra from a JEOL JMS-01SG-2 mass spectrometer.

In general, reactions were carried out under an argon atmosphere unless otherwise mentioned.

(1*S,5*R**,6*S**)-6-[(2-Methoxyethoxy)methoxy]bicyclo-[3.3.0]octan-3-one (11).** To a stirred solution of the MEM ether **10**[4] (6.63 g, 31 mmol) in Me_2SO–H_2O (50:1, 20 mL) was added NBS (7.00 g, 39 mmol) at 0 °C, and the reaction mixture was allowed to stir for 20 min at room temperature. The reaction was quenched by the addition of saturated $NaHCO_3$(aq). The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine. Concentration of the dried solvent ($MgSO_4$) afforded the oily residue, which was purified by silica gel column chromatography (petroleum ether–AcOEt, 2:1) to yield the bromohydrin (6.20 g). A mixture of the bromohydrin (6.20 g), Bu_3SnH (6.30 mL, 24 mmol), and a catalytic amount of AIBN in benzene (50 mL) was heated at reflux for 0.5 h and then diluted with ether. The organic layer was successively washed with 5% NaOH(aq) and brine. Concentration of the dried solvent ($MgSO_4$) afforded an oily residue, which was purified by silica gel column chromatography (AcOEt–petroleum ether, 1:1) to yield the alcohol (3.95 g). To a stirred suspension of the alcohol (3.95 g) and Celite (7.4 g) in methylene chloride (50 mL) was added PCC (7.40 g, 34 mmol) at room temperature. The resulting brown suspension was stirred for 2 h and then filtered through a short pad of Florisil. An additional ether was used to rinse the Florisil. The filtrate was concentrated in vacuo to afford the nearly pure ketone **11** as a pale yellow oil: 3.50 g (50% overall yield from **10**); IR (neat) 2925, 1735, 1450, 1400, 1360, 1240, 1200, 940, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20–2.90 (10 H, m), 3.41 (3 H, s), 3.50–3.90 (4 H, m), 4.06–4.40 (1 H, m), 4.73 (2 H, AB q, J = 7 Hz); mass spectrum, m/e 228 (M^+), 205, 185, 171, 153, 140, 123, 105, 95, 89; mass spectrum, m/e calcd for **11** ($C_{12}H_{20}O_4$, M^+) 228.1361, found 228.2361.

Methyl (1*S,5*R**,6*S**)-6-[(2-Methoxyethoxy)methoxy]-bicyclo[3.3.0]octane-3-carboxylate (5).** A solution of LDA (13.5 mmol) in THF (38 mL) was added to a suspension of (methoxymethyl)triphenylphosphonium chloride (5.00 g, 14.6 mmol) in toluene (35 mL) at 0 °C, and the mixture was stirred for 5 min at the same temperature. To the Wittig reagent was then added the ketone **11** (2.78 g, 12.9 mmol) in toluene (30 mL), and the whole reaction mixture was allowed to stir at 0 °C for 0.5 h. The reaction was quenched by the addition of saturated NH_4Cl(aq). The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine. Concentration of the dried solvent ($MgSO_4$) afforded the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether, 3:1) to yield the enol ether **12** as a nearly colorless oil [3.03 g, 80% yield based on the recovery of the ketone **11** (0.76 g)]. A solution of **12** (1.28 g, 5 mmol) in AcOH–H_2O–THF (3:1:1, 5 mL) was stirred at room temperature for 5 days, followed by the concentration of the volatile solvents in vacuo. The residual oil was dissolved in ether, and the ether layer was successively washed with saturated $NaHCO_3$(aq) and brine. Concentration of the dried solvent ($MgSO_4$) afforded the aldehyde **13** as a pale yellow oil, whose solution in ether (40 mL) was added to a mixture of CrO_3 (1.60 g, 16 mmol), concentrated H_2SO_4 (1.78 mL, 32 mmol), and $MnSO_4 \cdot 5H_2O$ (7.72 g, 32 mmol) in H_2O (40 mL). The reaction mixture was stirred at room temperature for 3 h, and then the ether layer was separated from the aqueous layer, which was further extracted with ether. The combined ether extracts were successively washed with water and brine. Concentration of the dried solvent ($MgSO_4$) afforded the crude carboxylic acid, which was treated with etheral diazomethane. Purification by silica gel column chromatography furnished the ester **5** as a mixture of the stereoisomers: nearly colorless oil; 866 mg (63% yield from **11**); IR (neat) 2940, 1730, 1460, 1430, 1360, 1235, 920, 850, 680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10–3.00 (11 H, m), 340 (3 H, s), 3.50–3.90 (4 H, m), 3.67 (3 H, s), 3.90–4.24 (1 H, m), 4.74 (2 H, s); mass spectrum, m/e 273 ($M^+ + 1$), 196, 183, 167; mass spectrum, m/e calcd for **5** ($C_{14}H_{25}O_5$, $M^+ + H$) 273.1701, found 273.1702, R_f 0.36 (**5a**), 0.45 (**5b**) (ether–petroleum ether, 1:1, two developments).

Typical Procedure for the Methylation Reaction of the Ester 5 to 14 and 15. LDA in THF (0.35 mmol, 2.70 mL) was added to a stirred solution of the ester **5** (218 mg, 0.8 mmol) in ether (15 mL) at −78 °C. After the mixture was stirred for 5 min at the same temperature, methyl iodide (0.14 mL, 2.4 mmol) was added. Then the mixture was gradually warmed up to 0 °C, and the reaction was quenched by the addition of saturated NH_4Cl(aq). The resulting aqueous layer was extracted with ether, and the combined ether extracts were washed with brine. Concentration of the dried solvent ($MgSO_4$) afforded the oily residue, which was purified by silica gel column chromatography (ether–petroleum ether, 1:1) to yield a mixture of **14** and **15**: nearly colorless oil; 182 mg (80% yield); IR (neat) 2950, 1730, 1460, 1370, 1250, 1110, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 (*exo*-Me), 1.30 (*endo*-Me), 1.06–3.14 (13 H, m), 3.40 (3 H, s), 3.68 (3 H, s), 3.90–4.24 (1 H, m), 4.73 (2 H, s); mass spectrum, m/e 286 (M^+), 227, 210, 197, 176, 166, 151, 137, 121, 110, 93, 89; mass spectrum, m/e calcd for **14** and **15** ($C_{15}H_{26}O_5$, M^+) 286.1780, found 286.1777.

Methyl (1*S,3*S**,5*R**,6*S**)-6-Hydroxy-3-methylbicyclo-[3.3.0]octane-3-carboxylate (22).** A solution of the MEM ether

(7) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 4119.

(8) Several lithium dialkylamides other than LDA were also employed as a strong base to examine the effects on the stereoselectivity on the alkylation reaction, indicating that LDA is the best for the present purpose.

(ca. 2.3:1 **14**/**15**; 87 mg, 0.32 mmol) in 1% H_2SO_4 (acetone–water, 7:1, 10 mL) was stirred at 50 °C for 2 days, and the reaction mixture was diluted with water. The aqueous layer was extracted with ether, and the combined ether extracts were successively washed with water and brine. Concentration of the dried solvent ($MgSO_4$) afforded an oily residue, which was purified by silica gel column chromatography to yield **22** (nearly colorless oil; 36 mg, 55% yield) together with the lactone **23** (nearly colorless oil; 14 mg, 24% yield). For **22**: IR (neat) 3400, 2950, 1720, 1460, 1370, 1315, 1290, 1100, 1070, 980, 870, 820, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.00–3.00 (11 H, m), 3.70 (3 H, s), 4.00–4.35 (1 H, m); mass spectrum, *m/e* 198 (M^+), 180, 166, 148, 139, 121, 101, 95, 93, 80; mass spectrum, *m/e* calcd for **22** ($C_{11}H_{18}O_3$, M^+) 198.1256, found 198.1253. The spectral data of **23** were as follows: IR (neat) 2950, 1725, 1460, 1360, 1160, 1100, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.20–3.00 (10 H, m), 4.70–4.88 (1 H, m); mass spectrum, *m/e* 166, 148, 139, 122, 107; mass spectrum, *m/e* calcd for **23** ($C_{10}H_{14}O_2$, M^+) 166.0994, found 166.0991.

Methyl (1*S,3*S**,5*R**)-3-Methyl-6-oxobicyclo[3.3.0]octane-3-carboxylate (2).** To a stirred suspension of the alcohol **22** (176 mg, 0.9 mmol) and Celite (381 mg) in methylene chloride (5 mL) was added PCC (381 mg, 1.9 mmol) at room temperature. The whole reaction mixture was stirred for 3 h under the same conditions, followed by filtration through a short pad of Florisil. Additional ether was used to rinse the Florisil. The filtrate was concentrated in vacuo to afford an oily residue, which was purified by silica gel column chromatography to yield 2 as a nearly colorless oil: 159 mg (90% yield); IR (neat) 2950, 1720, 1460, 1190, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.50–3.20 (10 H, m), 3.70 (3 H, s); mass spectrum, *m/e* 196, 168, 164, 151, 140, 137, 109, 96, 93, 81; mass spectrum, *m/e* calcd for **2** ($C_{11}H_{16}O_3$, M^+) 196.1099, found 196.1099.

Acknowledgment. We are grateful to Miwa Sawahata for her technical assistance. We also thank Kazuko Uchida for mass spectrometric measurements.

Registry No. (±)-**1**, 55123-33-6; (±)-**2**, 87419-62-3; (±)-**5a**, 87351-11-9; (±)-**5b**, 87351-12-0; **6**, 87351-13-1; (±)-**10**, 87351-14-2; (±)-**11**, 87351-15-3; (±)-**12**, 87351-16-4; (±)-**14**, 87351-17-5; (±)-**15**, 87351-18-6; (±)-**18**, 87351-19-7; **19**, 87351-20-0; (±)-**20**, 87351-21-1; (±)-**22**, 87351-22-2; (±)-**23**, 87419-63-4.

Synthesis of Two Macrolide Aggregation Pheromones from the Flat Grain Beetle, *Cryptolestes pusillus* (Schönherr)[1]

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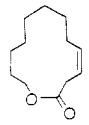
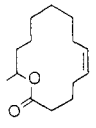
The flat grain beetle, *Cryptolestes pusillus* (Schönherr), is a major world-wide pest of stored grain.[2] We have recently isolated two macrolides (**1** and **2**) from the volatiles and frass of this insect.[3,4] The most abundant macrolide, **1**, is an aggregation pheromone for the flat grain beetle, while the other macrolide, **2**, appears to act as a synergist. We report the stereoselective syntheses of **1** and enantiomers of **2**.

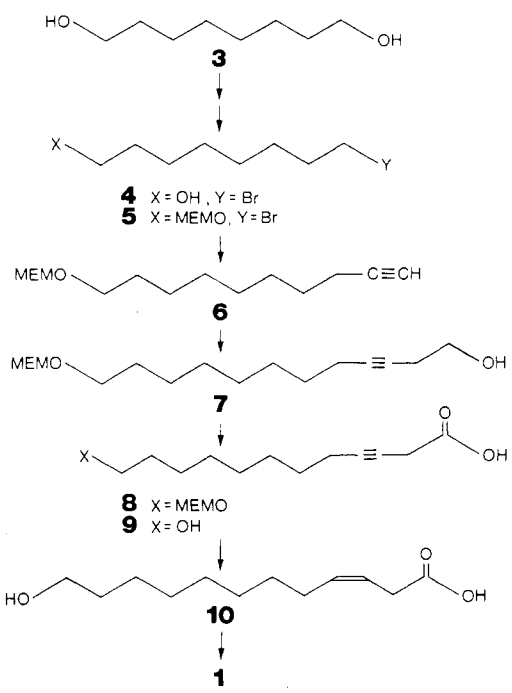


1



2

Scheme I



In the initial structural identification of **1**, there was some uncertainty as to whether the unsaturation was *E* or *Z*. Thus, the synthesis of **1** was designed so that either *E* or *Z* unsaturation could be introduced in one of the last steps, via stereoselective reduction of an alkyne. In the synthesis of **1**, the route as far as intermediate **7** was patterned after that of Maurer and Grieder,[5] who have reported the THP analogue of **7**. Thus, 1,8-octanediol (**3**) was converted to 8-bromo-1-octanol (**4**) with 48% aqueous HBr.[5] The hydroxyl of **4** was protected by reaction with (β-methoxyethoxy)methyl chloride, yielding the (β-methoxyethoxy)methyl ether **5** (Scheme I). Reaction of **5** with lithium acetylide in THF/HMPA[6] gave terminal alkyne **6**, which was converted to the homopropargylic alcohol **7** by sequential reaction with ethyl magnesium bromide and ethylene oxide.[7] Oxidation of **7** with pyridinium dichromate in DMF gave only low yields of the desired β,γ-unsaturated carboxylic acid. Inverse addition[8] of an acetone solution of **7** to Jones reagent at 0 °C gave the β,γ-unsaturated acid **8** in moderate yield, with no detectable hydrolysis of the MEM protecting group. Removal of the MEM protecting group was achieved with THF/H_2O/HCl, conditions which did not isomerize the unsaturation. The resulting hydroxy acid, **9**, was stereoselectively reduced with P-2 nickel[9] to the (*Z*)-β,γ-unsaturated hydroxy acid **10**. Cyclization of **10** to **1** was achieved

(1) This work was presented in part at the combined meeting of the Entomological Societies of America, Canada, and Ontario, November 29–December 3, 1982, in Toronto, and at the Chemical Institute of Canada annual meeting in Calgary, Alberta, June 5–8, 1983.

(2) Barak, A. V.; Harein, P. K. *J. Econ. Entomol.* **1981**, *74*, 197. Mueller, D. K. Insects Unlimited Inc., Indianapolis, IN, personal communication.

(3) The manuscript describing isolation, identification, and bioassay of **1** and **2** is in preparation and will be submitted to the *Journal of Chemical Ecology*.

(4) J.W.W. has also identified **2** in the frass and volatiles of *Cryptolestes ferrugineus* (Stephens).

(5) Maurer, B.; Grieder, A. *Helv. Chim. Acta* **1977**, *60*, 1155.

(6) Beckmann, W.; Doerjer, G.; Logemann, E.; Merkel, C.; Schill, G.; Zurcher, C. *Synthesis* **1975**, 423.

(7) Brandsma, . "Preparative Acetylenic Chemistry", 1st ed.; Elsvier: New York, 1971; p 32.

(8) Holland, B. C.; Gilman, N. W. *Synth. Commun.* **1974**, *4*, 203.

(9) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553.

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