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The Synthesis of 9-Substituted *p*-Mentha-1,8(10)-diene Derivatives

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The chemical conversion of (+)-limonene (**1**) and (−)-perillyl alcohol (**10**) into 9-substituted *p*-mentha-1,8(10)-diene derivatives is described. The lithiated species of **1** and **10** were easily obtained in good yields, by using *sec*-butyl lithium in *N*, *N*, *N'*, *N'*-tetramethylethylenediamine. The reaction of the lithiated species (A and B) with various electrophiles was completed within 1—2 h to give 9-substituted *p*-mentha-1,8(10)-diene derivatives. The stereochemistry of the chiral center of the starting material was retained in the products.

9-Hydroxy-*p*-mentha-1,8(10)-diene (**8**) was also obtained by another short sequence of steps. Oxidation of the phenylthio derivative (**7**) gave the sulfoxide (**9**). Treatment of **9** with trimethyl phosphite afforded **8**.

Keywords——synthesis; lithiation; limonene; perillyl alcohol; electrophile

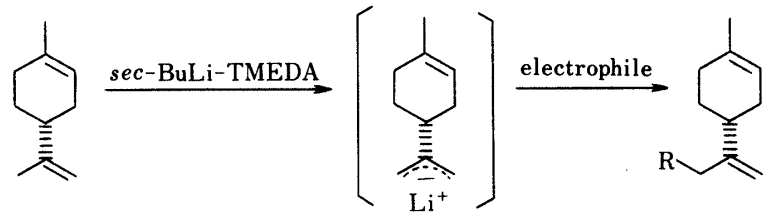
As a part of our synthetic studies on biologically active compounds containing a five-membered ring, such as prostaglandins, brefeldin A and methylenomycin A, we have already reported the Rh-complex-catalyzed stereoselective conversion[1] of (+)-limonene (*p*-mentha-1,8(10)-diene) derivatives to optically active *cis*-3,4-disubstituted cyclopentanones. For further work on this conversion, various limonene derivatives, particularly C-9 substituted *p*-mentha-1,8(10)-diene derivatives were required.

Crawford[2] previously reported the selective lithiation at the C-9 position of *p*-mentha-1,8(10)-diene (**1**) using *n*-butyl lithium (*n*-BuLi) in *N*, *N*, *N'*, *N'*-tetramethylethylenediamine (TMEDA), followed by alkylation. However, their method required a long time for lithiation(overnight), and the yield of alkylation or oxygenation was unsatisfactory. It was found that *sec*-butyl lithium (*sec*-BuLi) in TMEDA was more effective than *n*-BuLi. In this paper, we wish to describe a facile and useful method for the synthesis of 9-substituted-*p*-mentha-1,8(10)-diene and 9-substituted-7-hydroxy-*p*-mentha-1,8(10)-diene derivatives[3] based on the use of *sec*-BuLi.

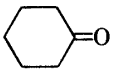
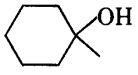
As shown in Table I, alkylations or thioalkylations of lithiated limonene (A) with various electrophiles afforded **2**—**6** in moderate yields (62—81%), except for the reaction of A with diphenyl disulfide. Compounds **2** and **3** obtained from the reaction of A with aldehydes were considered to be mixtures of diastereoisomers (Table I, entries 1 and 2).

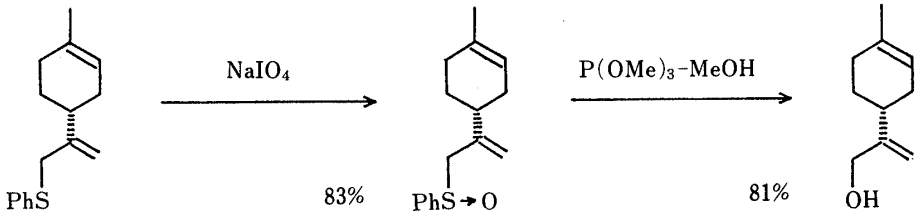
So far, there is no practical method for the synthesis of 9-oxygenated *p*-mentha-1,8(10)-diene. Previously, Sewata[4] and Nomura[5] obtained (+)-9-hydroxy-*p*-mentha-1,8(10)-diene (**8**) in 1 and 13% yields by oxidation of **1** with SeO_2 or $Pb(OAc)_4$, respectively. The reaction of A with oxygen, followed by a reductive work-up, afforded **8** in 48% yield. In this reaction, no racemization at the C-4 position occurred, based on a comparison of the optical rotation of **8** with that of an authentic sample. Thus, this method seems to be more practical for the synthesis of 9-oxygenated *p*-mentha-1,8(10)-diene. The phenylthio derivative (**7**) was also converted to **8** in good yield (Chart 1). The sulfoxide (**9**), derived from **7** by oxidation with $NaIO_4$, was easily converted to **8** by heating with trimethyl phosphite through a 2,3-

TABLE I. Yields of 9-Substituted *p*-Mentha-1,8(10)-diene (**2**–**8**)



1 **A** **2**–**8**

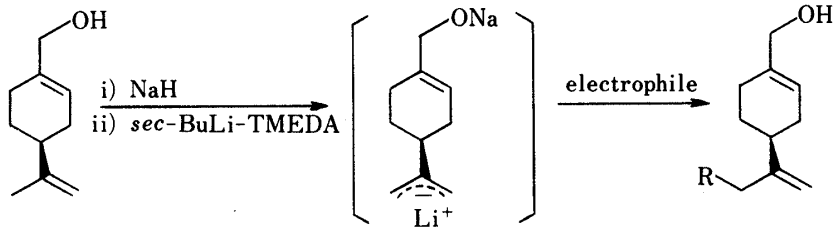
Entry	Electrophiles	Compd. No.	R	Yield (%)
1	PhCHO	**2**	PhCH(OH)–	81
2	CH_3CH_2CHO	**3**	$CH_3CH_2CH(OH)$–	62
3		**4**		73
4	*n*-BuBr	**5**	*n*-Bu–	79
5	MeSSMe	**6**	MeS–	72
6	PhSSPh	**7**	PhS–	25
7	O_2	**8**	HO–	48



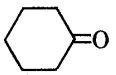
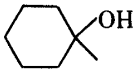
7 **9** **8**

Chart 1

TABLE II. Yields of 9-Substituted 7-Hydroxy-*p*-mentha-1,8(10)-diene (**11**–**16**)



10 **B** **11**–**16**

Entry	Electrophiles	Compd. No.	R	Yield (%)
1	PhCHO	**11**	PhCH(OH)–	45
2	CH_3CH_2CHO	**12**	$CH_3CH_2CH(OH)$–	25
3		**13**		72
4	*n*-BuBr	**14**	*n*-Bu–	40
5	PhSSPh	**15**	PhS–	23
6	O_2	**16**	HO–	23

sigmatropic process.[6]

The direct lithiation of (−)-7-hydroxy-*p*-mentha-1,8(10)-diene (**10**) at the C-9 position was performed by the dianion method. The dianion intermediate (B) was prepared by treatment of **10** with sodium hydride, followed by lithiation with *sec*-BuLi in TMEDA. As shown in Table II, B was converted to compounds **11**—**16** by a method similar to that used for the alkylation of limonene to compounds **2**—**8**.[7] Compounds **11** and **12** were considered to be mixtures of diastereoisomers, like compounds **2** and **3**.

Experimental

Infrared (IR) spectra were measured with a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on a JEOL JNM-PS-100 spectrometer using Me_4Si as an internal standard. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-SL polarimeter. Sodium hydride (60% in oil suspension) and *sec*-BuLi (1.1 M in hexane solution, Aldrich Chemical Co.) were used for metallation. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. The usual work-up refers to quenching with *tert*-BuOH, dilution with water, extraction with AcOEt, washing with satd. brine, drying over anhydrous Na_2SO_4, filtration, and evaporation *in vacuo*.

General Procedure for the Preparation of (*R*)-9-Substituted-*p*-mentha-1,8(10)-diene (2—7)——A well-stirred solution of **1** (1.0 g, 7.35 mmol) in TMEDA (1.88 g, 16.2 mmol) was cooled to −60 °C, then *sec*-BuLi (14.7 ml, 16.2 mmol) was added dropwise. After being stirred for 10—20 min, the mixture was allowed to warm to room temperature during 20 min, then stirred for an additional 1 h. The mixture was cooled to −60 °C again, and the electrophile (18.4 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C for 1 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (10 g).

(*R*)-9-[(ξ)-(α-Hydroxybenzyl)]-*p*-mentha-1,8(10)-diene (2)[8]——**1** (1.0 g, 7.35 mmol) and benzaldehyde (1.95 g, 18.4 mmol) were used for the reaction. The fraction eluted with 25% AcOEt in hexane (v/v) from a silica gel column was collected, and removal of the solvent *in vacuo* afforded **2** (1.44 g, 81%) as a colorless oil. IR (neat): 3425, 3040, 1640, 1604, 1500, 900 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, s, C_1–Me), 2.38 (1H, s, OH), 4.74 (1H, m, Ph–CH–), 4.89, 4.92 (1H each, s, $=CH_2$), 5.38 (1H, m, C_2–H), 7.30 (5H, s, aromatic H). MS *m/e*: 242 (M^+), 224, 107. *Anal.* Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.29; H, 9.23.

(*R*)-9-[(ξ)-1-Hydroxypropan-1-yl]-*p*-mentha-1,8(10)-diene (3)[8]——**1** (1.0 g, 7.35 mmol) and propanal (1.07 g, 18.4 mmol) were used for the reaction. The fraction eluted with 20% AcOEt in hexane (v/v) from a silica gel column was collected, and removal of the solvent *in vacuo* afforded **3** (0.89 g, 62%) as a colorless oil. IR (neat): 3375, 3100, 1640, 1450, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 1.65 (3H, s, C_1–Me), 3.64 (1H, m, $-C\underline{H}(OH)-$), 4.85, 4.90 (1H each, s, $=CH_2$), 5.38 (1H, m, C_2–H). MS *m/e*: 194 (M^+), 176. *Anal.* Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.59; H, 11.15.

(*R*)-9-(1-Hydroxycyclohexan-1-yl)-*p*-mentha-1,8(10)-diene (4)——**1** (1.0 g, 7.35 mmol) and cyclohexanone (1.44 g, 18.4 mmol) were used for the reaction. The fraction eluted with 10% acetone in hexane (v/v) from a silica gel column was collected, and removal of the solvent *in vacuo* afforded **4** (1.0 g, 73%) as a colorless oil. IR (neat): 3400, 3080, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, s, C_1–Me), 4.86, 4.94 (1H each, s, $=CH_2$), 5.42 (1H, m, C_2–H). MS *m/e*: 234 (M^+), 216, 136. *Anal.* Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.70; H, 11.43.

(*R*)-9-Butyl-*p*-mentha-1,8(10)-diene (5)——**1** (1.0 g, 7.35 mmol) and butyl bromide (2.52 g, 18.4 mmol) were used for the reaction. The fraction eluted with hexane from a silica gel column was collected, and removal of the solvent *in vacuo* afforded **5** (1.12 g, 79%) as a colorless oil. $[\alpha]_D^{21}$ +59° (*c*=1.65, EtOH). IR (neat): 3080, 1642, 1450, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 1.65 (3H, s, C_1–Me), 4.69, 4.71 (1H each, s, $=CH_2$), 5.38 (1H, m, C_2–H). MS *m/e*: 192 (M^+), 121. *Anal.* Calcd for $C_{14}H_{24}$: C, 86.51; H, 13.49. Found: C, 86.75; H, 13.20.

(*R*)-9-Methylthio-*p*-mentha-1,8(10)-diene (6)——**1** (1.0 g, 7.35 mmol) and dimethyl disulfide (1.73 g, 18.4 mmol) were used for the reaction. The fraction eluted with hexane from a silica gel column was collected, and removal of the solvent *in vacuo* afforded **6** (0.96 g, 72%) as a colorless oil. $[\alpha]_D^{21}$ +103° (*c*=1.25, EtOH). IR (Nujol): 3075, 3000, 1635, 1430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, s, C_1–Me), 1.98 (3H, s, SMe), 3.14 (2H, s, $-CH_2S-$), 4.88 (2H, s, $=CH_2$), 5.40 (1H, m, C_2–H). MS *m/e*: 182 (M^+), 135. *Anal.* Calcd for $C_{11}H_{18}S$: C, 72.46; H, 9.95. Found: C, 72.18; H, 10.00.

(*R*)-9-Phenylthio-*p*-mentha-1,8(10)-diene (7)——**1** (0.80 g, 5.9 mmol) and diphenyl disulfide (3.2 g, 14.7 mmol) were used for the reaction. The fraction eluted with hexane from a silica gel column was collected, and removal of the solvent *in vacuo* afforded **7** (0.36 g, 25%) as a colorless oil. $[\alpha]_D^{21}$ +64° (*c*=0.7, EtOH). IR (neat): 3075, 3010, 1640, 1585, 1438, 903 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, s, C_1–Me), 3.58 (2H, s, $-CH_2S-$), 4.86, 4.93 (1H each, s, $=CH_2$), 5.40 (1H, m, C_2–H), 7.24 (5H, m, aromatic H). MS *m/e*: 244 (M^+), 135. *Anal.* Calcd for $C_{16}H_{20}S$: C, 78.63; H, 8.25. Found: C, 78.40; H, 8.20.

(*R*)-9-Hydroxy-*p*-mentha-1,8(10)-diene (8)——Metallation of **1** (0.80 g, 5.9 mmol) was performed in the same manner as described above. The solution was cooled to −60 °C, and stirred under an oxygen atmosphere. The

reaction mixture was allowed to warm to 0 °C for 1 h. After being quenched with *tert*-BuOH (5 ml), the reaction mixture was diluted with water (50 ml), and then AcOEt (30 ml) and 25% sodium sulfite solution (10 ml) were added. The resulting two-phase mixture was stirred for 24 h at room temperature. The organic layer was separated, and the aqueous solution was extracted with AcOEt (30 ml × 3). The combined extracts were washed with satd. brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (10 g). The fraction eluted with 25% AcOEt in hexane yielded **8** (0.43 g, 48%) as a colorless oil. $[\alpha]_D^{21}$ +103° (c=1.50, EtOH). lit., $[\alpha]_D^{30}$ +104° (c=0.33, EtOH).[2] IR and ^{1}H-NMR spectra were consistent with those of an authentic sample.

(*R*)-9-Phenylsulfinyl-*p*-mentha-1,8(10)-diene (9)——Sodium periodate (0.30 g, 1.38 mmol) was added to a solution of **7** (0.24 g, 0.98 mmol), acetone (5 ml) and water (5 ml). After being stirred for 9 h at 40—50 °C, the reaction mixture was diluted with water (30 ml) and satd. brine (10 ml), then extracted with AcOEt (40 ml × 3). The combined extracts were washed with satd. brine (50 ml), and dried over anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo*, the crude product was purified by column chromatography on silica gel (5 g). The fraction eluted with AcOEt yielded **9** (0.23 g, 90%), mp 50—52 °C. IR (neat): 3060, 1630, 1582, 1480, 1440, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, s, C_1–Me), 3.52 (2H, m, $-CH_2SO-$), 4.90, 5.05 (1H each, s, $=CH_2$), 5.37 (1H, m, C_2–H), 7.50 (5H, m, aromatic H). MS m/e: 260 (M^+), 243, 135. *Anal.* Calcd for $C_{16}H_{22}OS$: C, 73.80; H, 7.74. Found: C, 73.59; H, 7.72.

8 from 9——Freshly distilled trimethyl phosphite (0.59 g, 3.2 mmol) was added dropwise under an argon atmosphere to a mixture of **9** (0.21 g, 0.80 mmol) and MeOH (5 ml). After being stirred for 9 h at 50 °C, the reaction mixture was poured into water satd. with $NaHCO_3$ (40 ml), and extracted with AcOEt (40 ml × 3). The combined extracts were washed with satd. brine (50 ml), and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (5 g). The fraction eluted with 25% AcOEt in hexane (v/v) yielded **8** (0.30 g, 81%) as a colorless oil.

General Procedure for the Preparation of (*S*)-9-Substituted 7-Hydroxy-*p*-mentha-1,8(10)-diene (11—15)——**10** (0.8 g, 5.3 mmol) was added dropwise to a suspension of sodium hydride (0.32 g, 7.9 mmol) in dry hexane (5 ml) at 5 °C. The mixture was stirred for an additional 1 h at 50 °C to give a pale yellow suspension, and then cooled −60 °C. After addition of TMEDA (1.28 g, 11.6 mmol), *sec*-BuLi (10.5 ml, 11.6 mmol) was added dropwise. The mixture was stirred for 10—20 min at −60 °C, and allowed to warm to room temperature for an additional 1 h to give a reddish-orange suspension. The mixture was cooled to −60 °C again, and the electrophile (13.2 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C during 1 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (10 g).

(*S*)-7-Hydroxy-9-[(ξ)-(α-hydroxybenzyl)]-*p*-mentha-1,8(10)-diene (11)[8]——**10** (0.8 g, 5.3 mmol) and benzaldehyde (1.39 g, 13.2 mmol) were used for the reaction. The fraction eluted with 14% acetone in benzene (v/v) from a silica gel column yielded **11** (0.87 g, 45%) as a colorless oil. IR (neat): 3350, 3040, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.80 (2H, br, OH × 2), 3.89 (2H, s, $-CH_2O-$), 4.74 (1H, t, J=6 Hz, $-C\underline{H}(OH)-$), 4.89 (2H, s, $=CH_2$), 5.64 (1H, m, C_2–H), 7.28 (5H, s, aromatic H). MS m/e: 250 (M^+), 232, 214, 150, 134. *Anal.* Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.90; H, 8.56.

(*S*)-7-Hydroxy-9-[(ξ)-1-hydroxypropan-1-yl]-*p*-mentha-1,8(10)-diene (12)[8]——**10** (1.0 g, 6.6 mmol) and propanal (0.95 g, 14.5 mmol) were used for the reaction. The fraction eluted with 11% acetone in hexane (v/v) from a silica gel column yielded **12** (0.34 g, 25%) as a colorless oil. IR (neat): 3340, 3080, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 2.92 (2H, br, OH × 2), 3.64 (1H, m, $-C\underline{H}(OH)-$), 3.95 (2H, s, $-CH_2O-$), 4.87, 4.90 (1H each, s, $=CH_2$), 5.69 (1H, br s, C_2–H). MS m/e: 210 (M^+), 192, 134. *Anal.* Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.07; H, 10.53.

(*S*)-7-Hydroxy-9-(1-hydroxycyclohexan-1-yl)-*p*-mentha-1,8(10)-diene (13)——**10** (0.7 g, 4.6 mmol) and cyclohexanone (1.13 g, 11.5 mmol) were used for the reaction. The fraction eluted with 20% AcOEt in hexane (v/v) from a silica gel column yielded **13** (0.83 g, 72%), mp 85—86 °C. IR (Nujol): 3320, 3080, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (2H, s, OH × 2), 3.98 (2H, s, $-CH_2O-$), 4.87, 4.93 (1H each, s, $=CH_2$), 5.70 (1H, m, C_2–H). MS m/e: 250 (M^+), 232, 214, 150, 134. *Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.55; H, 10.41.

(*S*)-9-Butyl-7-hydroxy-*p*-mentha-1,8(10)-diene (14)——**10** (0.8 g, 5.3 mmol) and butyl bromide (1.80 g, 13.2 mmol) were used for the reaction. The fraction eluted with 20% AcOEt in hexane (v/v) from a silica gel column yielded **14** (0.606 g, 40%) as a colorless oil. $[\alpha]_D^{21}$ −80° (c=1.5, EtOH). IR (neat): 3325, 3080, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7 Hz, $-CH_2C\underline{H}_3$), 1.74 (1H, s, OH), 3.98 (2H, s, $-CH_2O-$), 4.73 (2H, s, $=CH_2$), 5.70 (1H, m, C_2–H). MS m/e: 208 (M^+), 190, 134. *Anal.* Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.76; H, 11.70.

(*S*)-7-Hydroxy-9-phenylthio-*p*-mentha-1,8(10)-diene (15)——**10** (0.8 g, 5.3 mmol) and diphenyl disulfide (2.9 g, 13.2 mmol) were used for the reaction. The fraction eluted with 20% AcOEt in hexane (v/v) from a silica gel column yielded **15** (0.317 g, 23%) as a colorless oil. $[\alpha]_D^{21}$ −46° (c=0.7, EtOH). IR (neat): 3350, 3090, 1640, 1595, 910 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (2H, s, $-CH_2S-$), 3.96 (2H, s, $-CH_2O-$), 4.85, 4.94 (1H each, s, $=CH_2$), 5.68 (1H, m, C_2–H), 7.25 (5H, m, aromatic H). MS m/e: 260 (M^+), 242, 150, 133. *Anal.* Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74. Found: C, 73.54; H, 7.50.

(*S*)-7,9-Dihydroxy-*p*-mentha-1,8(10)-diene (16)——Metallation of **10** (0.8 g, 5.3 mmol) was performed in a manner similar to that described above. The reaction mixture was cooled to −60 °C, and stirred under an oxygen

atmosphere, then allowed to warm to 0 °C during 1 h. After work-up as described for the preparation of **8**, the crude product was purified by column chromatography on silica gel (10 g). The fraction eluted with 20% acetone in hexane (v/v) yielded **16** (0.20 g, 23%) as a colorless oil. $[\alpha]_D^{21}$ −79° (c=0.7, EtOH). IR (neat): 3340, 3100, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (2H, br s, OH × 2), 3.96, 4.12 (2H each, s, $-CH_2O-$ × 2), 4.89, 5.04 (1H each, s, $=CH_2$), 5.70 (1H, m, C_2–H). MS m/e: 168 (M^+), 150, 132. *Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.95. Found: C, 71.16; H, 9.69.

References and Notes

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7) The lithiation of **10** with *n*-BuLi in TMEDA resulted in the formation of a complex mixture.
8) Compounds **2**, **3**, **11** and **12** were considered to be mixtures of diastereoisomers.