Pergamon

Tetrahedron 54 (1998) 13155–13166

TETRAHEDRON

Correlation between Optical Rotation Sign and Conformation of γ-Butyrolactones. An Empirical Correlation Rule to Predict Optical Activity and Stereochemistry of γ-Butyrolactones

Fu-An Kang* and Cheng-Lie Yin

Department of Chemistry, Beijing Normal University, Beijing 100875, P. R. China

Received 16 June 1997; revised 2 February 1998; accepted 1 September 1998

Abstract: A series of *trans*-4,5-disubstituted-γ-butyrolactones are found to adopt different conformations by ^{1}H NMR spectroscopy, whose optical rotation signs are found to depend on the conformations they assume. An empirical correlation rule is proposed for the prediction of optical activity and stereochemistry of γ-butyrolactones, which is confirmed by the X-ray analyses of (+)- and (-)-γ-butyrolactones. © 1998 Elsevier Science Ltd. All rights reserved.

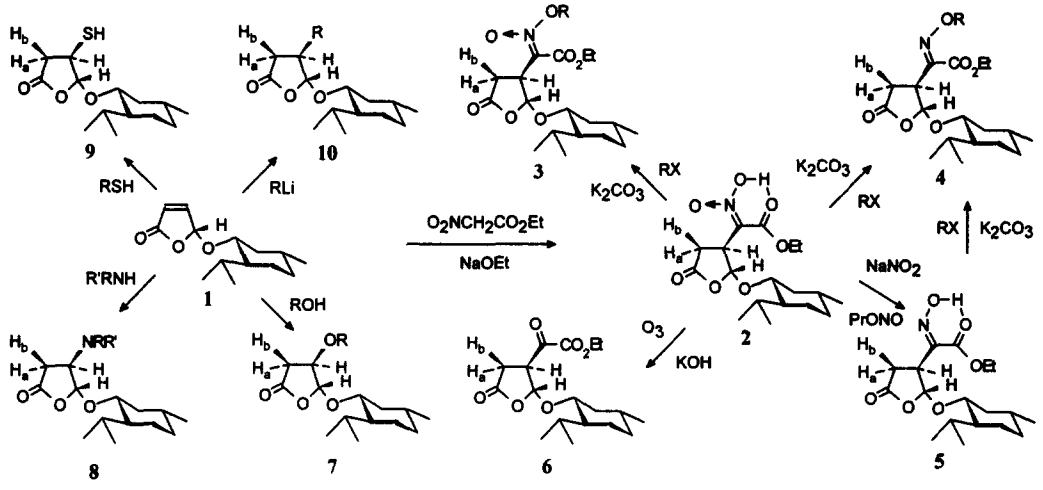
Since the beginning of the study of optically active substances, many attempts have been made to devise a method for calculating the magnitude of optical rotation or at least to learn how to predict the sign of rotation. As a result, some empirical rules[1] regarding the optical activities have been found. Empirical methods[2] for the prediction of the sign and magnitude of rotation based on bond refractions and polarizabilities of groups in a molecule have been suggested, which have given fairly good results in many cases. Although the cause of optical activity has been interpreted by both theoretical and nontheoretical methods,[3] the nature of optical activity, or the correlation of the chiral molecule's structure with the sign and value of its optical rotation is still a problem that has not been solved. In this paper, we report our discovery of the correlation between optical rotation sign and conformation of γ-butyrolactones.

RESULTS AND DISSCUSSION

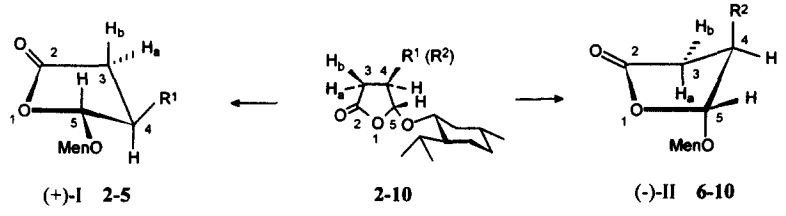
Recently, in the study of the physical and spectral properties of a series of *trans*-4,5-disubstituted-γ-butyrolactones (**2-10**) derived from (*R*)-(-)-5-[(1*R*)-menthyloxy]-2(5*H*)-furanone[4] (**1**) (Scheme 1), we found that the optical rotation signs of the γ-butyrolactones correlate strictly with the relative order of the chemical shifts of the C_3 methylene protons H_{3a} and H_{3b} in the range of δ 2.0-3.0, as the substituent on the C_4 atom changes from one series to another. That is, the optical rotation signs of compounds **2**,[5] **3**,[5] **4**,[5] **5** are all positive, where H_{3a} resonates at higher magnetic field than H_{3b}, or $\delta H_{3a} < \delta H_{3b}$; while the optical rotation signs

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00817-5

of compounds **6**, **7**, **8**,[6] **9**,[7] **10**[8] are all negative, where H_{3a} resonates at lower magnetic field than H_{3b}, or $\delta H_{3a} > \delta H_{3b}$ (Table 1).[9] This phenomenon appears somewhat confusing and unlikely considering that there is only one difference, the C_4 substituent, among these compounds. The possibility of the anisotropic effects of the C_4 substituents can be removed, because, although compounds **2-5** and compound **6** all have double bonds (C=N or C=O bonds), they still lead to a different relative order of the chemical shifts of H_{3a} and H_{3b}.



Scheme 1



R^1 = $C(NO_2H)CO_2Et$, $C(NO_2R)CO_2Et$, $C(NOR)CO_2Et$, $C(NOH)CO_2Et$
R^2 = $COCO_2Et$, OR, NRR', SR, Alkyl
MenO = menthyloxy

Figure 1

There seems to be only one interpretation for the interesting transposition of the chemical shifts of the C_3 methylene protons H_{3a} and H_{3b}, which is that the two series of compounds **2-5** and compounds **6-10** assume different conformations, respectively. γ-Butyrolactone is a five-membered ring and it is not surprising to think that it should adopt an envelope conformation. The preference for coplanarity of the lactone group[10] implies that the stable conformations of the γ-butyrolactone are restricted to an enantiomeric pair,[11] in which the C_4

Table 1

Compound	R	Mp, °C	[α] (c, Solvent) [a]	δH_{3a}	δH_{3b}	$\Delta\delta$ [c]	$J_{3a,3b}$	$J_{3a,4}$	$J_{3b,4}$	$J_{4,5}$	Ref
2		146-147	+52 (1.0, $CHCl_3$)	2.64	2.94	+0.30	17.4	11.5	3.3	0	5
3a	CH_3	93-94	+64 (1.0, $CHCl_3$)	2.58	2.86	+0.28	16.6	11.5	3.4	0	5
3b	C_2H_5	71.5-72.5	+68 (1.0, $CHCl_3$)	2.55	2.83	+0.28	16.6	11.2	3.4	0	5
3c	C_3H_7	81-82	+66 (1.0, $CHCl_3$)	2.57	2.84	+0.27	16.6	11.2	3.4	0	5
3d	C_4H_9	89-90	+61 (1.0, $CHCl_3$)	2.56	2.83	+0.27	16.6	11.2	3.6	0	5
3e	C_9H_{19}	54-55	+53 (1.0, $CHCl_3$)	2.57	2.84	+0.27	16.6	11.2	3.5	0	5
3f	$C_{12}H_{25}$	53.5-55.5	+50 (1.0, $CHCl_3$)	2.56	2.83	+0.27	16.6	11.3	3.4	0	5
3g	$PhCH_2$	97-98	+48 (1.0, $CHCl_3$)	2.61	2.89	+0.28	16.6	11.0	3.4	0	5
3h	*c*-C_5H_9	80-81	+66 (1.0, $CHCl_3$)	2.56	2.76	+0.20	16.6	10.7	3.6	0	5
3i	*c*-C_6H_{11}	73-75	+64 (1.0, $CHCl_3$)	2.56	2.78	+0.22	16.6	10.7	3.4	0	5
3j	C_8H_{17}	56-58	+57 (0.78, CH_2Cl_2) [b]	2.56	2.84	+0.28	16.6	11.2	3.5	0	[d]
3k	$C_{16}H_{33}$	51-53	+47 (0.84, CH_2Cl_2) [b]	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[d]
3l	allyl	67-68	+27 (0.61, CH_2Cl_2) [b]	2.60	2.88	+0.28	16.4	11.2	3.4	0	[d]
3m	*i*-C_3H_7	55-56	+59 (0.81, CH_2Cl_2) [b]	2.56	2.79	+0.23	16.4	10.8	3.5	0	[d]
3n	*s*-C_4H_9	36-42	+55 (0.92, CH_2Cl_2) [b]	2.55	2.80	+0.25	15.6	10.8	3.4	0	[d]
4a	*c*-C_5H_9	oil	+104 (2.18, hexane)	2.36	2.76	+0.40	16.0	10.8	3.7	1.8	5
4b	*c*-C_6H_{11}	oil	+94 (0.72, hexane)	2.36	2.76	+0.40	16.0	10.8	3.7	1.8	5
4c	allyl	oil	+91 (0.28, CH_2Cl_2) [b]	2.40	2.87	+0.47	16.4	11.4	3.6	1.2	[d]
4d	*s*-C_4H_9	oil	+87 (0.76, CH_2Cl_2) [b]	2.35	2.80	+0.45	15.6	10.8	3.4	1.2	[d]
4e	CH_3	oil	+231 (1.0, hexane)	2.38	2.68	+0.43	16.6	11.4	3.6	1.5	[d]
5		121-122	+118 (1.0, $CHCl_3$)	2.36	2.88	+0.52	17.2	11.5	3.2	0	[d]
6		58-61	-134 (0.83, CH_2Cl_2)	2.97	2.78	-0.19	18.0	9.4	4.8	2.2	[d]
7a	C_2H_5	93-94	-146 (1.1, $CHCl_3$)	2.79	2.45	-0.34	17.8	6.0	1.4	0	[d]
7b	C_3H_7	92-93	-132 (0.86, $CHCl_3$)	2.77	2.45	-0.32	18.0	6.0	1.6	0	[d]
7c	C_4H_9	73-74	-128 (0.81, CH_2Cl_2)	2.79	2.45	-0.34	17.8	6.0	1.2	0	[d]
7d	$PhCH_2$	86-87	-230 (1.0, hexane)	2.81	2.52	-0.29	18.0	5.8	1.4	0	[d]
7e	allyl	74-75	-182 (1.0, $CHCl_3$)	2.79	2.47	-0.32	17.8	5.8	1.6	0	[d]
8a	H, $PhCH_2$	100.6-102.7	-101 (1.0, $CHCl_3$) [b]	2.8	2.3	-0.5	15	7	3	0	6
8b	CH_3, $PhCH_2$	oil	-109 (1.0, $CHCl_3$) [b]	2.7	2.1	-0.6	15	8	2	0	6
8c	$(CH_2)_4$	134.6-134.8	-150 (1.0, $CHCl_3$) [b]	[e]	[e]	[e]	[e]	[e]	[e]	2	6
8d	$(CH_2)_5$	114.9-115.6	-149 (1.0, $CHCl_3$) [b]	[e]	[e]	[e]	[e]	[e]	[e]	2	6
8e	$(CH_2)_2O(CH_2)_2$	109.4-110.2	-142 (1.0, $CHCl_3$) [b]	[e]	[e]	[e]	[e]	[e]	[e]	2	6
8f	C_2H_5, C_2H_5	oil	-148 (1.0, $CHCl_3$) [b]	[e]	[e]	[e]	[e]	[e]	[e]	2	6
8g	H, C_4H_9	semisolid	-134 (1.0, $CHCl_3$) [b]	[e]	[e]	[e]	[e]	[e]	[e]	0	6
9	Ph	77.8-78	-62 (1.0, $CHCl_3$) [b]	3.04	2.38	-0.66	15	8	3	0	7
10a	CH_3	78.2-79.8	-147 (0.9, $CHCl_3$) [b]	2.82	2.09	-0.73	17.6	8.2	4.0	2.2	8
10b	$(CH_3S)_3C$	oil	-89 (1.8, $CHCl_3$) [b]	[e]	[e]	[e]	[e]	[e]	[e]	0	8

[a] Unless otherwise indicated, the specific rotations were measured at 578 nm at 25 °C. [b] Determined at 589 nm at 20 or 25 °C. [c] $\Delta\delta = \delta H_{3b} - \delta H_{3a}$. [d] The present paper. [e] Not assigned or given in the original literature.

atom is either below (conformation I) or above (conformation II) the lactone plane (Figure 1). The hydrogens or substituents at C_3, C_4 and C_5 atoms are expected to adopt *quasi*-axial or *quasi*-equatorial positions.[12]

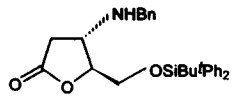
In conformation I, H_{3b}, H_4 and H_5 are *quasi*-axial protons, while H_{3a}, menthyloxy and R^1 adopt the *quasi*-equatorial positions. On the contrary, in conformation II, H_{3a}, menthyloxy and R^2 assume the *quasi*-axial positions, while H_{3b}, H_4 and H_5 are *quasi*-equatorial protons. According to the proposed model[13] of the anisotropic effect of the carbonyl group, the *quasi*-equatorial protons of the C_3 methylenes in both conformations I and II should be in the shielding region of the C_2 carbonyl group while the corresponding *quasi*-axial protons should be in the deshielding region. As a result, in the two conformations I and II, the *quasi*-axial proton on the C_3 methylene is expected to resonate at lower magnetic field than the corresponding *quasi*-equatorial proton. Since for compounds **2-5**, the relative order of the chemical shifts of H_{3a} and H_{3b} is $\delta H_{3a} < \delta H_{3b}$, therefore it is self-evident that compounds **2-5** all assume conformation I. And because for compounds **6-10**, the relative order of the chemical shifts of H_{3a} and H_{3b} is $\delta H_{3a} > \delta H_{3b}$, it can also be inferred that compounds **6-10** all adopt conformation II.

Apparently, this result agrees with the previous observations that in steroidal α-acetoxy,[14] α-halo ketones[15] and α-bromo cyclohexanones,[16] the α-protons of the carbonyl groups resonate at lower magnetic fields when axial than when equatorial.

In both conformations I and II, the geminal coupling constants of the C_3 methylene protons H_{3a} and H_{3b} alter in a narrow range, or $^2J_{3a,3b}$ = 15-18 Hz. In conformation I, there are three vicinal couplings which include one coupling of the *quasi*-equatorial H_{3a} and the *quasi*-axial H_4 with the coupling constants, $^3J_{3a,4}$ = 10.8-11.5 Hz, and two couplings of the *quasi*-axial protons H_{3b}, H_4 and H_5 with the coupling constants $^3J_{3b,4}$ = 3.2-3.7 Hz and $^3J_{4,5}$ = 0-1.8 Hz. In this case, the *quasi*-axial H_{3b} is deshielded 0.2-0.5 ppm by the C_2 carbonyl group with respect to the *quasi*-equatorial H_{3a}. In conformation II, there are also three vicinal couplings which consist of one coupling of the *quasi*-axial H_{3a} and the *quasi*-equatorial H_4 with the coupling constants $^3J_{3a,4}$ = 5.8-9.4 Hz, and two couplings of the *quasi*-equatorial protons H_{3b}, H_4 and H_5 with the coupling constants $^3J_{3b,4}$ = 1.2-1.8 Hz and $^3J_{4,5}$ = 0-2.2 Hz. In this case, the *quasi*-axial H_{3a} is deshielded 0.2-0.7 ppm by the C_2 carbonyl group with respect to the *quasi*-equatorial H_{3b}. It should be noted that these data of this five-membered ring are in contrast to those of a six-membered ring where the coupling constant of the vicinal axial-axial protons is usually much larger than that of the vicinal axial-equatorial protons,[17] and an equatorial proton is generally deshielded 0.1-0.7 ppm by the C-C bonds with respect to the corresponding axial proton.[18]

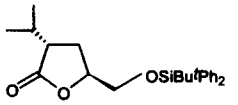
If the substituents R^1, R^2 and MenO were replaced with hydrogens, it would be obvious that conformer I and conformer II are enantiomers, or that one is the mirror image of the other. Since the absolute configuration of C_4 and C_5 atoms are the same in both conformations I and II, it appears to be reasonable and significant that the optical rotation signs of the γ-butyrolactones depend on the conformations they assume rather than on the substituents on the lactone ring (although R^1 and R^2 belong to a variety of substituents and MenO is a

menthyloxy that contains three chiral centers), in other words, conformer I creates a right-handed rotation, while conformer II results in a left-handed rotation.[19]



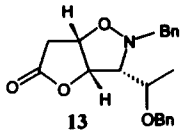
11

$[\alpha]^{20}_D$ +15.3 (*c* 1.08, $CHCl_3$)



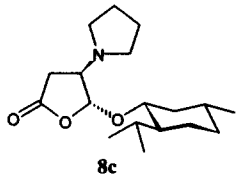
12

$[\alpha]^{20}_D$ +13.2 (*c* 1.00, $CHCl_3$)



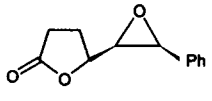
13

$[\alpha]^{20}_D$ +53.4 (*c* 2.01, $CHCl_3$)



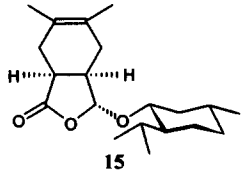
8c

$[\alpha]^{20}_D$ -150.1 (*c* 1.0, $CHCl_3$)



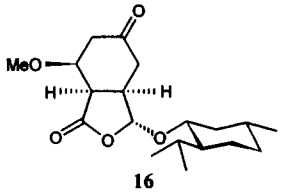
14

$[\alpha]^{25}_D$ -79 (*c* 1.0, $CHCl_3$)



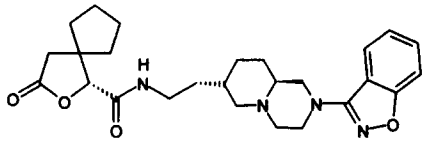
15

$[\alpha]_D$ -214.1 (*c* 1.0, *n*-hexane)



16

$[\alpha]^{20}_D$ -199.9 (*c* 1.00, CH_2Cl_2)



17

$[\alpha]_D$ -14.76 (*c* 0.42, CH_2Cl_2)

Figure 2

The correlation between optical rotation sign and conformation of chiral γ-butyrolactones are unequivocally confirmed by the X-ray analyses of (+)-γ-butyrolactones **11**[20], **12**[21] and **13**[22], and (-)-γ-butyrolactones **8c**[6], **14**[23], **15**[9], **16**[9] and **17**[24] (Figure 2). The OPTEP plots of (+)-γ-butyrolactones **11-13** clearly show that their lactone rings assume the expected conformation I with the C_4 atom deviating below the lactone plane, whereas the ORTEP plots of (-)-γ-butyrolactones **8c** and **14-17** indicate that their lactone rings adopt the predicted conformation II with the C_4 atom deviating above the lactone ring.

On the basis of these interesting and important findings, we propose an empirical correlation rule for the prediction of optical activity and stereochemistry of γ-butyrolactones:

(1) If the relative order in chemical shifts of the C_3 methylene protons of a γ-butyrolactone is $\delta H_{3a} < \delta H_{3b}$, then it must assume conformation I and it must be a dextrorotatory compound;

(2) If the relative order in chemical shifts of the C_3 methylene protons of a γ-butyrolactone is $\delta H_{3a} > \delta H_{3b}$, then it must adopt conformation II and it must be a levorotatory compound;

(3) If the optical rotation sign of a γ-butyrolactone is positive, then it must assume conformation I;

(4) If the optical rotation sign of a γ-butyrolactone is negative, then it must adopt conformation II.

Because of the widespread occurrence of γ-butyrolactone rings in natural products, especially in molecules that possess diverse biological activity,[25] we think this empirical correlation rule will be useful to the prediction of optical activity and stereochemistry of such compounds.

In conclusion, a series of *trans*-4,5-disubstituted-γ-butyrolactones are found to adopt different conformations by ^1H NMR spectroscopy. The optical rotation signs of these γ-butyrolactones are found to correlate with their conformations. An empirical correlation rule is accordingly proposed for the prediction of optical activity and stereochemistry of γ-butyrolactones, which is confirmed by the X-ray analyses of (+)- and (-)-γ-butyrolactones. Further investigations on this subject are currently in progress.

EXPERIMENTAL SECTION

Elemental analyses were obtained on a Perkin-Elmer 240C micro analyzer. Infrared spectra were recorded on a Hitachi 260-50 spectrometer. ^1H and ^{13}C NMR spectra were performed at 200 MHz on a Varian-200 spectrometer in $CDCl_3$ with chemical shifts in ppm downfield from TMS and coupling constants in hertz. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter. Melting points (uncorrected) were taken on a Yanaco MP-500 apparatus. The syntheses and characterization of compounds **1**, **2**, **3a-3i**, and **4a-4b** were reported in the preceding paper.[5]

General Procedure for Preparation of Compounds 3 and 4. Compound **2** (0.74 g, 2 mmol) and finely ground anhydrous K_2CO_3 (0.28 g, 2 mmol) were mixed in DMF (9 mL). To this well stirred suspension was added an alkyl halide (2 mmol). The progress of the reaction was monitored by TLC. Soon after completion of the reaction, the mixture was dissolved in ether and washed with water and dried (Na_2SO_4). Removal of solvent furnished crude products which were further purified by recrystallization from light petroleum ether or by column chromatograghy on silica gel using a mixture of light petroleum ether and ethyl acetate (8:1) as the eluent affording compounds **3**, and **4** (where secondary or allyl halides were employed).

(*Z*)-(+)-*n*-Octyl nitronic ester of (4*S,5*R*)-4-(1'-nitro-1'-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (3j):** white crystals; mp 56-58 °C; $[\alpha]^{25}_{589}$ +56.8° (*c* 0.78, CH_2Cl_2); IR (KBr) 1760, 1725, 1640 cm^{-1}; ^1H NMR δ 0.76-1.16 (m, 14H), 1.2-1.5 (m, 16H), 1.63 (m, 4H), 2.16 (m, 2H), 2.56 (dd, 1H, *J* = 16.6, 11.2), 2.84 (dd, 1H, *J* = 16.6, 3.5), 3.41 (dd, 1H, *J* = 10.4, 4.2), 3.75 (dd, 1H, *J* = 11.2, 3.5), 4.10

(t, 2H), 4.33 (q, 2H), 5.39 (s, 1H); Anal. Calcd for $C_{26}H_{45}NO_7$: C, 64.60; H, 9.32; N, 2.90. Found: C, 64.48; H, 9.30; N, 3.15.

(*Z*)-(+)-*n*-Hexadecyl nitronic ester of (4*S,5*R*)-4-(1'-nitro-1'-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (3k):** white crystals; mp 51-53 °C; $[\alpha]^{25}_{589}$ +46.5° (*c* 0.84, CH_2Cl_2); IR (KBr) 1760, 1730, 1640 cm^{-1}; Anal. Calcd for $C_{34}H_{61}NO_7$: C, 68.57; H, 10.25; N, 2.35. Found: C, 68.44; H, 10.30; N, 2.25.

(*Z*)-(+)-Allyl nitronic ester of (4*S,5*R*)-4-(1'-nitro-1'-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (3l):** white crystals; mp 67-68 °C; $[\alpha]^{25}_{589}$ +27.4° (*c* 0.61, CH_2Cl_2); IR (KBr) 1755, 1735, 1640 cm^{-1}; ^1H NMR δ 0.7-1.3 (m, 15H), 1.35 (t, 3H), 1.65 (m, 2H), 2.14 (m, 2H), 2.60 (dd, 1H, *J* = 16.4, 11.2), 2.88 (dd, 1H, *J* = 16.4, 3.4), 3.40 (dd, 1H, *J* = 10.6, 4.4), 3.75 (dd, 1H, *J* = 11.2, 3.4), 4.33 (q, 2H), 4.62 (d, 2H, *J* = 5.8), 5.27 (dd, 1H, *J* = 10.2, 1.4), 5.35 (dd, 1H, *J* = 17.5, 1.4), 5.39 (s, 1H), 5.91 (m, 1H, *J* = 17.5, 10.2, 5.8); ^{13}C NMR δ 14.2, 16.1, 21.0, 22.1, 23.0, 25.4, 31.7, 33.2, 34.1, 43.0, 47.1, 48.1, 61.9, 65.8, 81.9, 103.2, 109.9, 119.1, 131.5, 158.5, 169.7; Anal. Calcd for $C_{21}H_{33}NO_7$: C, 61.31; H, 8.03; N, 3.41. Found: C, 61.10; H, 8.05; N, 3.41.

(*Z*)-(+)-*iso*-Propyl nitronic ester of (4*S,5*R*)-4-(1'-nitro-1'-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (3m):** white crystals; mp 55-56 °C; $[\alpha]^{25}_{589}$ +59.4° (*c* 0.81, CH_2Cl_2); IR (KBr) 1760, 1725, 1640 cm^{-1}; ^1H NMR δ 0.71-1.23 (m, 15H), 1.25 (d, 6H), 1.35 (t, 3H), 1.65 (m, 2H), 2.56 (dd, 1H, *J* = 16.4, 10.8), 2.79 (dd, 1H, *J* = 16.4, 3.5), 3.42 (dd, 1H, *J* = 10.6, 4.4), 3.74 (dd, 1H, *J* = 10.8, 3.5), 4.33 (q, 2H), 5.03 (m, 1H), 5.40 (s, 1H); ^{13}C NMR δ 14.0, 15.9, 20.8, 21.5, 21.9, 22.0, 22.8, 25.2, 31.4, 33.4, 33.9, 42.8, 47.0, 48.0, 61.6, 68.5, 81.6, 103.0, 109.6, 158.3, 169.3; Anal. Calcd for $C_{21}H_{35}NO_7$: C, 61.02; H, 8.47; N, 3.39. Found: C, 61.23; H, 8.58; N, 3.45.

(*Z*)-(+)-(*RS*)-*sec*-Butyl nitronic ester of (4*S,5*R*)-4-(1'-nitro-1'-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (3n):** white crystals; mp 36-42 °C; $[\alpha]^{25}_{589}$ +55.4° (*c* 0.92, CH_2Cl_2); IR (KBr) 1740, 1700, 1635 cm^{-1}; ^1H NMR δ 0.7-1.1 (m, 15H), 1.15 (d, 3H), 1.35 (t, 3H), 1.4-1.9 (m, 6H), 2.15 (m, 2H), 2.55 (dd, 1H, *J* = 15.6, 10.8), 2.80 (dd, 1H, *J* = 15.6, 3.4), 3.41 (dd, 1H, *J* = 10.6, 4.2), 3.75 (dd, 1H, *J* = 10.8, 3.4), 4.34 (q, 2H), 4.88 (m, 1H), 5.38 (s, 1H); ^{13}C NMR δ 9.4, 14.0, 15.8, 19.1, 20.8, 21.9, 22.8, 25.2, 28.5, 31.4, 33.3, 33.9, 42.8, 47.0, 48.0, 61.7, 73.2, 81.6, 103.0, 109.7, 158.3, 169.6; Anal. Calcd for $C_{22}H_{37}NO_7$: C, 61.83; H, 8.67; N, 3.28. Found: C, 61.60; H, 8.65; N, 3.22.

(*Z*)-(+)-*O*-Allyloxime of (4*S,5*R*)-4-(1'-nitroso-1'-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-**

dihydro-2(5*H*)-furanone (4c): a colorless oil; $[\alpha]^{25}_{589}$ +91.3° (*c* 0.28, CH_2Cl_2); IR (neat) 1795, 1740, 1720, 1650, 1595 cm^{-1}; ^1H NMR δ 0.7-1.3 (m, 14H), 1.37 (t, 3H), 1.65 (m, 2H), 2.19 (m, 2H), 2.40 (dd, 1H, *J* = 16.4, 11.4), 2.87 (dd, 1H, *J* = 16.4, 3.6), 3.45 (dd, 1H, *J* = 10.6, 4.2), 3.63 (ddd, 1H, *J* = 11.4, 3.6, 1.2), 4.35 (q, 2H), 4.60 (d, 2H, *J* = 5.8), 5.26 (dd, 1H, *J* = 10.2, 1.4), 5.32 (dd, 1H, *J* = 17.5, 1.4), 5.53 (d, 1H, *J* = 1.2), 5.91 (m, 1H, *J* = 17.5, 10.2, 5.8); ^{13}C NMR δ 14.0, 16.0, 21.0, 22.1, 23.0, 25.3, 31.5, 32.4, 34.1, 42.8, 48.1, 49.4, 62.0, 65.7, 81.6, 110.7, 118.8, 131.6, 153.4, 159.9, 169.7; Anal. Calcd for $C_{21}H_{33}NO_6$: C, 63.80; H, 8.35; N, 3.54. Found: C, 63.65; H, 8.33; N, 3.50.

(*Z*)-(+)-*O*-(*RS*)-*sec*-Butyloxime of (4*S,5*R*)-4-(1'-nitroso-1'-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (4d):** a colorless oil; $[\alpha]^{25}_{589}$ +86.8° (*c* 0.76, CH_2Cl_2); IR (neat) 1795, 1740, 1590 cm^{-1}; ^1H NMR δ 0.7-1.15 (m, 15H), 1.21 (d, 3H), 1.36 (t, 3H), 1.58 (m, 6H), 2.20 (m, 2H), 2.35 (dd, 1H, *J* = 15.6, 10.8), 2.80 (dd, 1H, *J* = 15.6, 3.4), 3.45 (dd, 1H, *J* = 10.6, 4.2), 3.62 (ddd, 1H, *J* = 10.8, 3.4, 1.2), 4.35 (q, 2H), 4.86 (m, 1H), 5.54 (d, 1H, *J* = 1.2); ^{13}C NMR δ 9.5, 14.0, 16.0, 19.2, 20.9, 22.1, 22.9, 25.3, 28.6, 31.5, 32.7, 34.7, 42.8, 48.1, 49.5, 61.9, 73.1, 81.4, 110.7, 153.5, 159.9, 169.7; Anal. Calcd for $C_{22}H_{37}NO_6$: C, 64.23; H, 9.00; N, 3.41. Found: C, 64.05; H, 8.95; N, 3.40.

(4*S,5*R*)-(+)-4-(1'-Nitroso-1'-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (5).** Compound **2** (15 mmol, 5.4 g), $NaNO_2$ (0.15 mol, 10 g) and PrONO (0.15 mol, 12 g) were mixed in DMSO (40 mL) under nitrogen.[26] After stirred in subdued light at 23-28 °C for 48h, the reaction mixture was quenched with ice and water (400 mL) to give the crude product. Recrystallization from ether and petroleum ether afforded white crystals (4.0 g, 78%) of **5**: mp 121-122 °C; $[\alpha]^{25}_{578}$ +118° (*c* 1.0, $CHCl_3$); IR (KBr) 3250, 1745, 1725, 1688, 1590 cm^{-1}; ^1H NMR δ 0.66-1.14 (m, 14H), 1.29 (t, 3H), 1.55 (m, 2H), 2.11 (m, 2H), 2.36 (dd, 1H, *J* = 17.2, 11.5), 2.88 (dd, 1H, *J* = 17.2, 3.2), 3.35 (dd, 1H, *J* = 10.5, 4.1), 3.53 (dd, 1H, *J* = 11.5, 3.2), 4.26 (q, 2H), 5.74 (s, 1H), 11.35 (br s, 1H); ^{13}C NMR δ 14.2, 16.2, 21.2, 22.4, 23.4, 25.7, 31.9, 32.5, 34.7, 43.5, 46.8, 50.1, 62.1, 81.6, 111.4, 153.9, 160.3, 171.7; Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.81; H, 8.23; N, 3.94. Found: C, 60.92; H, 8.26; N, 3.95.

(*Z*)-(+)-*O*-Methyloxime of (4*S,5*R*)-4-(1'-nitroso-1'-carbethoxymethyl)-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (4e).** Compound **5** (0.5 g, 1.4 mmol) and finely ground anhydrous K_2CO_3 (0.19 g, 1.4 mmol) were mixed in DMF (10 mL). To this well stirred suspension was added methyl iodide (1.4 mmol). After stirred at room temperature for 48h, the mixture was dissolved in ether and washed with water and dried (Na_2SO_4). Removal of solvent under reduced pressure furnished a colorless oil of **4e**: $[\alpha]^{25}_{578}$ +230.5° (*c* 1.0, hexane); IR (neat) 1740, 1720, 1650, 1580 cm^{-1}; ^1H NMR δ 0.65-1.35 (m, 14H), 1.38 (t, 3H), 1.63 (m, 2H), 2.19 (m, 2H), 2.38 (dd, 1H, *J* = 16.6, 11.4), 2.86 (dd, 1H, *J* = 16.6, 3.6), 3.45 (dd, 1H, *J* = 10.6, 4.2), 3.62 (ddd,

1H, J = 11.4, 3.6, 1.5), 3.72 (s, 3H), 4.35 (q, 2H), 5.52 (d, 1H, J = 1.5); ^{13}C NMR δ 13.5, 15.6, 20.4, 21.6, 22.6, 24.9, 31.0, 31.9, 33.7, 42.4, 47.7, 49.0, 51.4, 61.4, 81.0, 110.3, 152.8, 159.3, 169.9; Anal. Calcd for $C_{19}H_{31}NO_6$: C, 61.79; H, 8.40; N, 3.79. Found: C, 61.92; H, 8.22; N, 3.73.

(4*R,5*R*)-(-)-4-Ethoxyoxalyl-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (6).** Compound **2** (2.0 g, 5.4 mmol) in methanol (25 mL) was treated with potassium hydroxide (0.33 g, 5.9 mmol) and stirred for 5 min to form the nitronate salt. Then the solution was cooled to 0 °C, and a stream of ozone-oxygen was passed through it.[27] The progress of the reaction was monitored by TLC. Soon after the completion of the reaction, the mixture was concentrated by rotary evaporation to a residue, which was dissolved in ether (50 mL) and washed with 20% NaOH, water, brine, and dried (Na_2SO_4). Removal of solvent gave crude product. Recrystallization from a mixture of petroleum ether and methylene chloride led to white crystals (1.5 g, 83%) of **6**: mp 58-61 °C; $[\alpha]^{25}_{589}$ -134° (*c* 0.83, CH_2Cl_2); IR (in nujol) 1790, 1760, 1750, 1730 cm^{-1}; ^{1}H NMR δ 0.7-1.3 (m, 14H), 1.40 (t, 3H), 1.65 (m, 2H), 2.10 (m, 2H), 2.78 (dd, 1H, J = 18.0, 4.8), 2.97 (dd, 1H, J = 18.0, 9.4), 3.55 (dd, 1H, J = 10.6, 4.2), 3.93 (ddd, 1H, J = 9.4, 4.8, 2.2), 4.38 (q, 2H), 5.86 (d, 1H, J = 2.2); ^{13}C NMR δ 13.9, 15.5, 20.8, 22.1, 22.9, 25.3, 29.2, 31.2, 34.1, 39.6, 47.5, 50.4, 63.3, 77.8, 99.4, 159.6, 173.5, 189.5; Anal. Calcd for $C_{18}H_{28}NO_6$: C, 63.53; H, 8.24. Found: C, 63.48; H, 8.21.

General Procedure for Preparation of Compounds 7. To a stirred solution of a primary alcohol (2 mL) in DMF (5 mL) was added a catalytic amount of metallic sodium. As soon as sodium disappeared, compound **1** (1.0 g, 4.2 mmol) was added and the resulting red color solution was stirred at room temperature for 3-24h until the red color faded (the red color might be caused by the resulting enol anion of the furanone). Then, the reaction mixture was dissolved in ether and washed with water and dried (Na_2SO_4). Removal of solvent afforded crude product that was further purified by recrystallization from light petroleum ether.

(4*R,5*R*)-(-)-4-Ethoxy-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (7a):** white crystals; mp 93-94 °C; $[\alpha]^{25}_{578}$ -146° (*c* 1.1, $CHCl_3$); IR (KBr) 1780 cm^{-1}; ^{1}H NMR δ 0.7-1.15 (m, 14H), 1.22 (t, 3H), 1.65 (m, 2H), 1.99 (m, 1H), 2.15 (m, 1H), 2.45 (dd, 1H, J = 17.8, 1.4), 2.79 (dd, 1H, J = 17.8, 6.0), 3.55 (q+dd, 3H), 3.90 (dd, 1H, J = 6.0, 1.4), 5.55 (s, 1H); ^{13}C NMR δ 15.1, 15.5, 20.8, 22.2, 22.9, 25.4, 31.3, 34.1, 34.2, 39.5, 47.6, 64.8, 76.8, 78.7, 102.8, 174.9. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.61; H, 9.86. Found: C, 67.55; H, 9.89.

(4*R,5*R*)-(-)-4-Propoxy-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (7b):** white crystals; mp 92-93 °C; $[\alpha]^{25}_{578}$ -132° (*c* 0.86, $CHCl_3$); IR (KBr) 1780 cm^{-1}; ^{1}H NMR δ 0.6-1.8 (m, 21H), 2.00 (m, 1H), 2.15 (m, 1H), 2.45 (dd, 1H, J = 18.0, 1.6), 2.77 (dd, 1H, J = 18.0, 6.0), 3.43 (t, 2H, J = 6.4), 3.54 (dd, 1H, J = 10.6, 4.0), 3.91 (dd, 1H, J = 6.0, 1.6), 5.55 (s, 1H); ^{13}C NMR δ 10.5, 15.5, 20.8, 22.2, 22.8, 25.5, 31.3, 34.1,

34.2, 39.6, 47.6, 71.1, 76.7, 78.9, 102.8, 174.9. Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.46; H, 10.07. Found: C, 68.35; H, 10.11.

(4*R,5*R*)-(-)-4-Butoxy-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (7c):** white crystals; mp 73-74 °C; $[\alpha]^{25}_{578}$ -128° (*c* 0.81, CH_2Cl_2); IR (KBr) 1780 cm^{-1}; ^1H NMR δ 0.7-1.8 (m, 23H), 2.00 (m, 1H), 2.15 (m, 1H), 2.45 (dd, 1H, *J* = 17.8, 1.2), 2.79 (dd, 1H, *J* = 17.8, 6.0), 3.47 (t, 2H, *J* = 6.2), 3.54 (dd, 1H, *J* = 10.0, 4.2), 3.91 (dd, 1H, *J* = 6.0, 1.2), 5.56 (s, 1H); ^{13}C NMR δ 13.7, 15.4, 19.0, 20.7, 22.1, 22.8, 25.3, 31.1, 31.5, 34.0, 34.1, 39.4, 47.4, 69.1, 76.5, 78.7, 102.7, 174.9. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.23; H, 10.26. Found: C, 69.35; H, 10.28.

(4*R,5*R*)-(-)-4-Benzyloxy-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (7d):** white crystals; mp 86-87 °C; $[\alpha]^{25}_{578}$ -230° (*c* 1.0, hexane); IR (KBr) 1780 cm^{-1}; ^1H NMR δ 0.7-1.5 (m, 18H), 1.65 (m, 2H), 2.00 (m, 2H), 2.52 (dd, 1H, *J* = 18.0, 1.4), 2.81 (dd, 1H, *J* = 18.0, 5.8), 3.52 (dd, 1H, *J* = 10.4, 4.2), 4.04 (dd, 1H, *J* = 5.8, 1.4), 4.58 (s, 2H), 5.58 (s, 1H); ^{13}C NMR δ 15.5, 20.8, 22.2, 22.9, 25.4, 31.2, 34.2, 39.5, 47.5, 71.6, 76.7, 78.4, 102.7, 127.7, 128.1, 128.5, 136.8, 174.8; Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.83; H, 8.67. Found: C, 72.88; H, 8.65.

(4*R,5*R*)-(-)-4-Allyloxy-5-[(1*R*)-menthyloxy]-3,4-dihydro-2(5*H*)-furanone (7e):** white crystals; mp 74-75 °C; $[\alpha]^{25}_{578}$ -182° (*c* 1.0, $CHCl_3$); IR (KBr) 1780, 1640 cm^{-1}; ^1H NMR δ 0.7-1.5 (m, 14H), 1.7 (m, 2H), 2.00 (m, 1H), 2.10 (m, 1H), 2.47 (dd, 1H, *J* = 17.8, 1.6), 2.79 (dd, 1H, *J* = 17.8, 5.8), 3.54 (dd, 1H, *J* = 10.4, 4.2), 4.03 (d+dd, 3H, *J* = 5.4; 5.8, 1.6), 5.22 (dd, 1H, *J* = 9.0, 1.4), 5.28 (dd, 1H, *J* = 17.2, 1.4), 5.58 (s, 1H), 5.88 (m, 1H, *J* = 17.2, 9.0, 5.4); ^{13}C NMR δ 15.5, 20.8, 22.2, 23.0, 25.4, 31.3, 34.1, 34.2, 39.5, 47.6, 70.2, 76.7, 78.3, 102.8, 117.7, 133.5, 174.7. Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.92; H, 9.46. Found: C, 69.10; H, 9.52.

ACKNOWLEDGMENT

Financial support provided by the National Natural Science Foundation of China, the Doctoral Program Foundation of the State Education Commission and the Allied Analysis Foundation of Beijing Zhongguancun is gratefully acknowledged.

REFERENCES AND NOTES

1. (a) Potapov, V. M. *Stereochemistry*, Mir Publishers: Moscow, 1978, pp. 200-207. (b) Mills, J. A.; Klyne, W. *Prog. Stereochem.* **1954**, *1*, 204. (c) Klyne, W.; Scopes, P. M. *Prog. Stereochem.* **1969**, *4*, 97. (d)

Eliel, E. L.; Willen, S. H. *Stereochemistry of Carbon Compounds*, Wiley: New York, 1994. (e) Kagan, H. B. *Determination of Configuration by Chemical Methods*, Vol 3, Georg Thieme Publishers: Stuttgart, 1977. (f) Schlenk, W. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 139.

2. (a) Brewster, J. H. *Top. Stereochem.* **1967**, *2*, 1. (b) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5475, 5483, 5493. (c) Davis, D. D.; Jensen, F. R. *J. Org. Chem.* **1970**, *35*, 3410. (d) Applequist, J. *J. Am. Chem. Soc.* **1973**, *95*, 8255, 8258.
3. For theoretical discussions, see: (a) Caldwell, D. J.; Eyring, H. *The Theory of Optical Activity*, Wiley: New York, 1971. (b) Kauzmann, W. *Quantum Chemistry*, Academic Press: New York, 1957. (c) Buckingham, A. D.; Stiles, P. J. *Acc. Chem. Res.* **1974**, *7*, 258. (d) Mason, S. F. *Q. Rev. Chem. Soc.* **1963**, *17*, 20. For nontheoretical discussions, see: ref. 1d. (e) Wheland, G. W. *Advanced Organic Chemistry*, 3rd, Wiley: New York, 1960, pp. 204-211.
4. Feringa, B. L.; De Jong, J. C. *J. Org. Chem.* **1988**, *53*, 1125.
5. Kang, F. -A.; Yin, C. -L.; She, S. -W. *J. Org. Chem.* **1996**, *61*, 5523.
6. De Lange, B.; Van Bolhuis F.; Feringa, B. L. *Tetrahedron* **1989**, *45*, 6799.
7. Feringa, B. L.; De Lange, B. *Tetrahedron* **1988**, *44*, 7213.
8. Jansen, J.; Feringa, B. L. *Synth. Commun.* **1992**, *22*, 1367.
9. In these γ-butyrolactones, H_{3a}, H_{3b} and H_4 protons constitute a typical ABX coupling system and are accordingly assigned on the basis of the relationship of their coupling constants: J_{gem} (15-18 Hz) > J_{cis} (11.5-5.8 Hz) > J_{trans} (1.2-4.8 Hz). The spectral data of *cis*-3,4-disubstituted-γ-butyrolactones confirm that the coupling constant of H_{3a} and H_4 is $J_{3a,4} = J_{cis} = 9.5$ Hz, see: De Jong, J. C.; Van Bolhuis, F.; Feringa, B. L. *Tetrahedron: Asymmetry* **1991**, *2*, 1247.
10. Mathieson, A. McL. *Tetrahedron Lett.* **1963**, 81.
11. Beecham, A. F. *Tetrahedron Lett.* **1968**, 3591.
12. Loudon, G. M. *Organic Chemistry,* Addison-Wesley: New York, 1984, p. 255.
13. Karabatsos, G. J.; Sonnichsen, G. C.; Hsi, N.; Fenoglio, D. J. *J. Am. Chem. Soc.* **1967**, *89*, 5067.
14. Williamson K. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 4623.
15. Nickon, A.; Castle, M. A.; Harada, R.; Berkoff, C. E.; Williams, R. O. *J. Am. Chem. Soc.* **1963**, *85*, 2185.
16. (a) Garbish, E. W. *J. Am. Chem. Soc.* **1964**, *86*, 1780. (b) Wellman, K. M.; Bordwell, F. G. *Tetrahedron Lett.* **1963**, 1703.
17. Anet, F. A. L. *J. Am. Chem. Soc.* **1962**, *84*, 1053.
18. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, John Wiley: New York, 1981.
19. Kang, F. -A.; Yin, C. -L. *J. Chem. Soc., Chem. Commun.* **1997**, 579.

20. (a) Collis, M. P; Hockless, D. C. R.; Perlmutter, P. *Tetrahedron Lett.* **1995**, *36*, 7133. (b) Collis, M. P.; Perlmutter, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2117.
21. Hanessian, S.; Abad-Grillo, T.; McNaughton-Smith, G. *Tetrahedron* **1997**, *53*, 6281.
22. Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1059.
23. Solladie-Cavallo, A.; Roche, D.; Bold, G.; Acemoglu, F.; Tintelnot-Blomley, M.; Fischer, J.; De Cian, A. *Tetrahedron: Asymmetry* **1996**, *7*, 1797.
24. Urban, F. J. *Tetrahedron: Asymmetry* **1994**, *5*, 211.
25. (a) Davies-Coleman, M. T.; Rivett, D. E. A. *Prog. Chem. Nat. Prod.* **1989**, *55*, 1. (b) Jefford, C. W.; Jaggi, D.; Sledeski, A. W.; Boukouvalas, J. in *Studies in Natural Products Chemistry*, Rahman, A., Ed., Elsevier: Amsterdam, 1989, Vol. 3, pp. 157-171. (c) Yoshioka, H.; Mabry, T. J.; Timmermann, B. N. *Sesquiterpene Lactones*, University of Tokyo Press: Tokyo, 1973. (d) Grieco, P. A. *Synthesis* **1975**, 67. (e) Heywood, H.; Harborne, J. B.; Turner, B. L. *The Biology and Chemistry of the Compositae*, Academic Press: London, 1977, Vol. 1 and 2. (f) Fischer, N. H.; Oliver, C. J.; Fischer, H. D. in *Progress in the Chemistry of Organic Natural Products*, Herz, B.; Grisebach, H.; Kirby, G. W., Eds., Springer-Verlag: New York, 1979, Vol. 38, Chapter 2. (g) Hoffman, H. M. R.; Rabe, J. *Angew Chem., Int. Ed. Engl.* **1985**, *24*, 94. (h) Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157.
26. This reaction condition was reported for the transformation of nitro compounds to carbonyl compounds. However in this case, the reaction converted compound **2** to compound **5** rather than compound **6**. See: Kornblum, N.; Wade, P. A. *J. Org. Chem.* **1973**, *38*, 1418.
27. It should be noted that this is the first mild ozonation converting a nitro compound to a carbonyl compound, for previous ozonations proceeded under strict and inconvenient conditions, see: (a) McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259. (b) Lehr, F.; Gonnermann, J.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 2274.