Tetrahedron Vol. 45, No. 9, pp. 2525 to 2540, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

DIASTEREOSELECTIVE REACTIONS OF 1,4-BIS(BROMOMAGNESIO)PENTANE WITH LACTONES AND CYCLIC ANHYDRIDES

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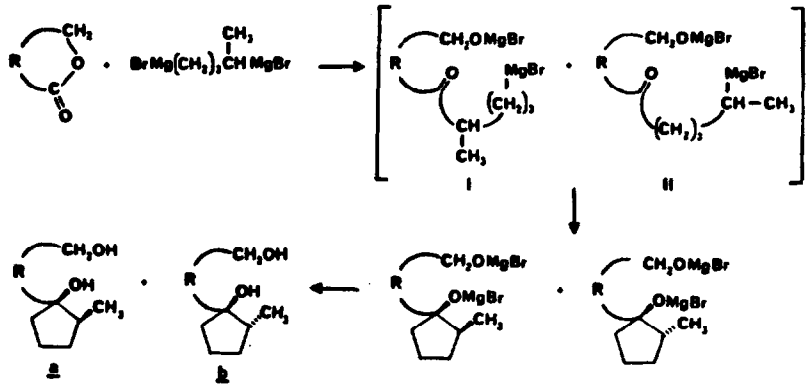
(*Received in USA* 13 *July* 1988)

Abstract - In the case of aromatic substrates, reactions of 1,4-bis-(bromomagnesio)pentane with lactones and isatoic anhydrides proceed with a remarkable stereochemical preference leading to the formation of the **trans** isomer. On the other hand, those with 4H-3,1-benzoxazin-4-ones provide mainly the **cis** isomer and, much more dramatic stereoselectivity has been observed in the cases of phthalic and 1,2-naphthalene dicarboxylic anhydrides. This difference in the stereochemical control of the intramolecular Grignard reaction can be attributed to the chelation between the groups in **ortho** position of the intermediate oxoalkyl magnesium compound. The alkoxy and the carboxylate seem to have an opposite effect. Furthermore, reactions of 1,4-bis(bromomagnesio)pentane with non-aromatic cyclic anhydrides yield preferentially the **trans** diastereoisomer.

Significant progress in the stereochemical control of organic reactions has been one of the major achievements in synthetic methodology over the last three decades[1]. Such control depends on the nature of organic reactions and on the nature of reagents and substrates. Particularly, in the case of the reaction of organometallic compounds with ketones, regioselectivity and stereoselectivity are due to steric, polar and coordinating effects of oxygen and nitrogen atoms with metals[2]. The bis Grignard reactions with carboxylic acid derivatives possess the common feature that consists in the double addition of the two nucleophilic centers to the same carbonyl group[3]. Furthermore, the reactions of 1,4-bis-(bromomagnesio)butane and 1,5-bis-(bromomagnesio)pentane mainly favour the formation of lactones, rather than open chain compounds, by the intramolecular reduction process or the intramolecular enolization process[4].

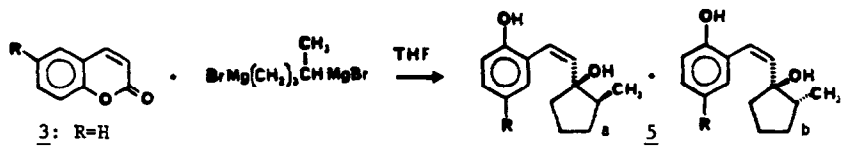
As it was previously described, 1,4-bis(bromomagnesio)pentane and 1,5-bis(bromomagnesio)hexane react with aliphatic and aromatic carboxylic acid esters with high diastereo-



Scheme I

selection leading preferentially to the formation of 1-substituted-**trans**-2-methylcycloalkanols[5]. A systematic study of the reactions of 1,4-bis(bromomagnesio)alkanes with carboxylic acid esters showed that **trans**-OH diastereoisomers are also formed[6]. These results suggest that the diastereoselection depends neither on the structure of esters nor on that of bis Grignard reagents. Therefore, we propose that the secondary function of 1,4-bis-(bromomagnesio)alkanes reacts faster with esters, whereas experiments with benzaldehyde showed a less pronounced chemioselectivity between the primary and secondary parts of bis Grignard reagents, leading to a mixture of alcohols.

The conceptual problem with the reaction is the efficacy of trapping the intermediate oxoalkyl Grignard reagent prior to its intramolecular reaction. Thus, in the present study, we wish to verify the stereochemistry of the reactions of 1,4-bis(bromomagnesio)pentane with lactones, cyclic anhydrides and other similar compounds, in order to examine factors that could influence the stereochemical control of the intramolecular Grignard reaction. The choice of lactones and cyclic anhydrides allows comparison between the carboxylate and the alcoholate group. The 1,4-bis(bromomagnesio)pentane was prepared in good yield from the corresponding dibromide or 1,4-dibromopentane[7] by using an excess of magnesium turnings in anhydrous tetrahydrofuran. The solution was kept at 25 °C for a few hours. The reactions occurred with an equimolar mixture of the bis Grignard reagent and the substrate (lactone, cyclic or isatoic anhydride, 4H-3,1-benzoxazin-4-one) at room temperature. We first studied the reactions of 1,4-bis(bromomagnesio)pentane with lactones, more precisely those with the phthalide (scheme I), and substituted coumarins (scheme II).



3: R=H
4: R=CH$_3$

5 6

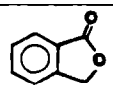
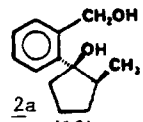
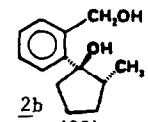
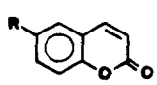
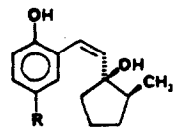
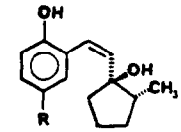
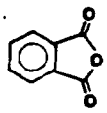
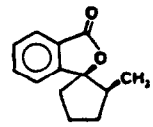
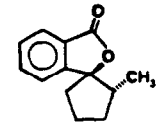
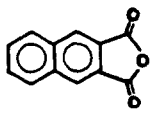
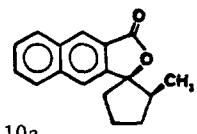
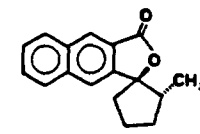
Scheme II

The reaction with the phthalide (1) in THF solution, produced, after hydrolysis, the corresponding 1-(o-hydroxymethylphenyl)-2-methylcyclopentanols (2a,b) in 85% yield. The ^{1}H NMR spectroscopy of the crude reaction mixture revealed that the **trans**-OH isomer (2b) was the major product (82%). Also, in the case of the same reaction with coumarins (3) and (4), **trans**-OH isomers (5b) and (6b) were formed with less pronounced stereoselectivity in a ratio **cis/trans** = 30/70 and 40/60 respectively (table I). It is important to specify that diastereoisomers (2a,b), (5a,b) and (6a,b) have been separated by flash chromatography unlike the other compounds of the present communication.

As previously reported[5], ^{1}H and ^{13}C spectroscopy distinguish the **cis** and **trans** isomers. ^{13}C NMR analysis reveal that the methyl carbon signals of the **trans** isomers have higher values than the **cis** isomers and, in ^{1}H NMR spectra, the protons of the methyl groups of the **cis** isomers appear downfield. These methods enable us to make a better identification of the products. In the present study, we can observe noticeable differences between diastereoisomers (2a) and (2b) in ^{1}H and ^{13}C NMR values of the methyl carbons. The chemical shift data of ^{13}C NMR δ (CH_3) is 12.70 ppm in the case of the **cis** cyclopentanol (2a), whereas the methyl carbon signals of the **trans** isomer (2b) appear at 19.95 ppm. Moreover, in ^{1}H NMR spectroscopy, the difference of structures is more pronounced where the protons of the methyl groups in the **cis** and the **trans** isomers appear at δ (CH_3) = 0.96 and 0.48 ppm respectively. Furthermore, we observe similar results in the case of ^{13}C NMR shifts for **cis** and **trans** cyclopentanols obtained from coumarins (3) and (4). However, ^{1}H NMR values show a less important disparity.

We have followed our research concerning the diastereoselectivity of the reaction of 1,4-bis(bromomagnesio)pentane, by using aromatic cyclic anhydrides as substrates. Phthalic anhydride (7) and 1,2-naphthalenedicarboxylic anhydride (9) have been treated in

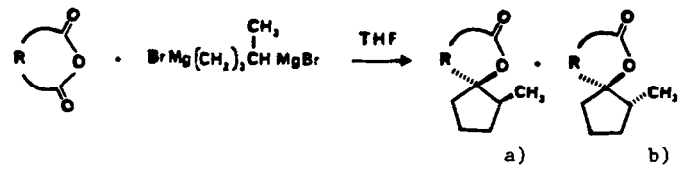
Table I. Diastereoisomer Distribution in the Reactions of Bis Grignard with Lactones and Cyclic Anhydrides.

Starting compound	Yield[1] (%)	Cis[2] (%)	δCH_3 ^1H	δCH_3 ^{13}C	Trans[2] (%)	δCH_3 ^1H	δCH_3 ^{13}C
 1	85	 2a (18)	0.96	12.70	 2b (82)	0.48	19.95
 3 R=H	55	 5a (30)	0.96	12.21	 5b (70)	0.89	17.05
4 R-CH_3	60	6a (40)	0.96	12.17	6b (60)	0.89	17.05
 7	70	 8a (100)	0.72	11.31	 8b (0)	0.58 (2a)	15.61 (2a)
 9	65	 10a (100)	0.73	11.78	 10b (0)		

1) Yields determined from isolated products. 2a) 8b was obtained by oxidation of 2b.
2b) Ratios of diastereoisomers determined by integration of 200-MHz ^1H NMR spectra and values given in parenthesis. Error estimated to be ± 5%.

similar experimental conditions (scheme III) and we found an opposite diastereoselectivity to that of lactones. The results show that only **cis** isomers (8a) and (10a) were isolated from each reaction with an extremely high stereoselectivity, after examination by ^1H and ^{13}C spectroscopy (table I).

In order to determine unambiguously their configuration, the spirolactone (8a) was reduced by using $LiAlH_4$[8] yielding the 1-(o-hydroxymethylphenyl)-c-2-methylcyclopentanol(2a) and, its **trans** diastereoisomer (2b) was oxidized into the spirolactone (8b) by using the Jones reagent[9]. Those transformations allowed us to establish more exactly the structures



7:R= 8

9:R= 10

11:R= 12

13:R= 14

15:R= 16

17:R= 18

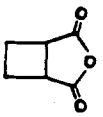
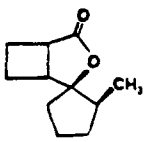
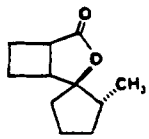
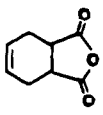
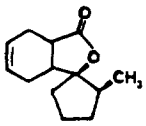
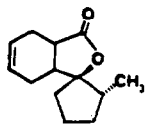
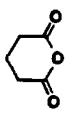
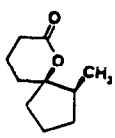
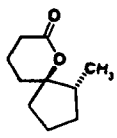
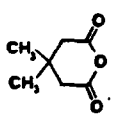
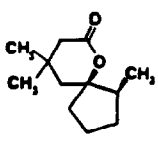
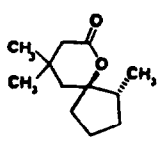
Scheme III

of the two diastereoisomers. ^{1}H and ^{13}C NMR data of the reduction product of compound (8a) are identical with those of the cis isomer (2a). In the case of the reduced spirolactone, the ^{1}H NMR chemical shift data of the methyl group δ (CH_3) appears at 0.95 ppm and is very close to that of the **cis** isomer (2a) where δ (CH_3) = 0.96 ppm.

This similarity in the structures is also confirmed by the analysis of ^{13}C NMR shifts of the methyl group. Thus, the methyl carbon signals of the **cis** isomer (2a) and the reduction product of (8a) present similar values, δ (CH_3) = 12.70 and 12.80 ppm respectively.

Thus, the reaction of 1,4-bis(bromomagnesio)pentane with phthalic anhydride (7) leads to the formation of the c-spiro[2-methylcyclopentane-1,1'-3H-isobenzofuran]-3'-one (8a) by analogy, **cis** configuration, is assigned to the spirolactone (10a) obtained from the same reaction with 1,2-naphthalene dicarboxylic anhydride (9). This remarkable influence of the stereochemistry of the intramolecular Grignard reaction can be attributed to the chelation between the groups in ortho position of the intermediate oxoalkylmagnesium com-

Table II. Diastereoisomer Distribution in the Reactions of Bis Grignard with Cyclic Anhydrides.

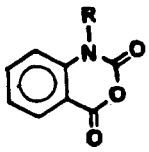
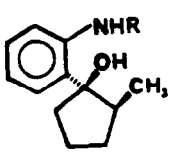
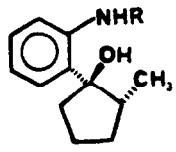
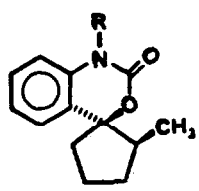
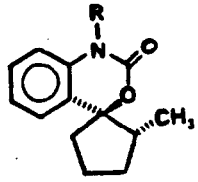
Starting compound	Yield[1] (%)	cis[2] (%)	δ CH_3 ^1H	δ CH_3 ^{13}C	Trans[2] (%)	δ CH_3 ^1H	δ CH_3 ^{13}C
							
11	69	12a (33)	0.91	12.36	12b (67)	0.88	16.68
							
13	64	14a (33)	1.14	13.39	14b (67)	0.96	17.71
							
15	38	16a (15)	1.00	13.00	16b	0.91	16.06
							
17	62	18a (23)	0.97	12.08	18b	0.89	16.30

1) Yields determined from isolated products. 2) Ratios of diastereoisomers determined by integration of 200-MHz ^1H NMR spectra and values given in parenthesis. Error estimated to be ±5%.

pound. It seems that the alkoxy[10a] and the carboxylate[10b] have an opposite effect in the case of aromatic compounds.

The analysis of Table I reveals that the diastereoisomer distribution in the reactions of 1,4-bis(bromomagnesio)pentane with aromatic lactones and cyclic anhydrides depends on their structural features. In the case of lactones, we observe a stereochemical preference leading to the formation of the **trans** diastereoisomer, whereas the reactions with phthalic and 1,2- naphthalene dicarboxylic anhydrides have favoured a stereoselectivity yielding exclusively the **cis** diastereoisomer.

Table III Distribution of 1-(o-Aminophényl)-2-méthylcyclopentanols and of spiro[2-alkylcyclopentane-1,4'-2H-3', 1'-benzoxazin]-2'-ones.

Starting compounds	Yield (%)		cis[2] (%)	δ CH_3 ppm		trans[2] (%)	δ CH_3 ppm	cis[2] (%)	δ CH_3 ppm	trans[2] (%)	δ CH_3 (ppm)
											
19: R=H	20	24a	(33)	0.98	24b	(67)	0.45				
20: R=CH_3	70	25a	(33)	0.95	25b	(67)	0.39	(33)	0.98	(67)	0.54
21: R=C_2H_5	65	26a	(35)	1.05	26b	(65)	0.49	(33)	0.98	(67)	0.54
22: R=C_3H_7	54	27a	(20)	0.84	27b	(80)	0.39	(42)	0.95	(58)	0.54
23: R=$CH_2C_6H_5$	52	28a	(40)	1.05	28b	(60)	0.54	(40)	1.03	(60)	0.54

In order to establish a more effective comparison between lactones and cyclic anhydrides, we extended our research to the reaction of the same bis Grignard reagent with non-aromatic rigid anhydrides (11,13,15 and 17) (scheme III). The desired corresponding spirolactones were obtained in good yields. As may be gathered in table II, all the reactions led preferentially to the **trans** diastereoisomer. However, the diastereoselectivity is more pronounced for compounds (15) and (17) where the **trans** isomers (16b) and (18b) are purified in 85% and 77% ratio respectively. For these last two cases, steric interactions seem to be more significant than those for compounds (11) and (13). The results of tables I and II show that the alkoxy and the carboxylate could influence the stereoselectivity in the cyclization step of the reactions of lactones and cyclic anhydrides with 1,4-bis(bromomagnesio)pentane.

As we previously described, aromatic cyclic anhydrides (7) and (9) produce the **cis** isomer, whereas non-aromatic cyclic anhydrides (11, 13, 15 and 17) provide mainly the **trans** isomer. Furthermore, to confirm the hypothesis concerning the effect of the structure of the substrate on the isomer distribution of the intramolecular Grignard reaction with 1,4-bis(bromomagnesio)pentane, we studied its reactions with different N-substituted isatoic anhydrides (19-23) and 2-substituted-4H-3,1-benzoxazin-4-ones (29-32), which have struc-

Table IV ^{13}C NMR Chemical Shifts of 1-Substituted-2-methylcyclopentanols (cis and trans)[1,2]

Compound:	R	C-1	C-2	C-3	C-4	C-5	CH_3
24[b] a	H	87.00 84.60	42.24 41.24	31.79 31.18	20.59 21.08	39.84 38.33	19.83 13.03
25[b] a	CH_3	87.59 84.75	40.98 39.51	31.83 31.18	20.07 20.59	38.24 36.65	19.96 13.08
26[b] a	C_2H_5	87.68 84.80	41.08 39.58	31.91 31.93	20.70 21.14	38.31 38.18	20.08 13.14
27[b] a	C_3H_7	87.51 84.73	45.51 45.62	31.93 31.25	20.68 20.01	39.57 41.02	20.01 13.09
28[b] a	$CH_2C_6H_5$	87.54 84.74	39.49 39.23	31.79 31.16	21.01 19.93	36.57 38.26	20.56 13.01
29[b] a	CH_3	92.82 91.56	42.17 43.81	30.76 31.44	20.46 20.55	34.49 39.41	16.97 11.86
30[b] a	C_2H_5	92.79 91.66	42.80 44.59	31.91 35.16	20.98 20.98	38.84 38.78	17.28 12.26
31[b] a	C_3H_7	92.86 91.90	45.35 44.55	31.98 35.18	21.03 20.12	42.77 40.04	17.43 12.32
32[b] a	$CH_2C_6H_5$	93.48 92.33	42.93 44.73	30.82 32.07	21.16 21.10	40.40 35.29	17.54 12.43

1) a = *cis*; b=*trans*; 2) chemical shifts are in δ from Me_4Si.

tural similarities with aromatic lactones (1, 3, 4) and cyclic anhydrides (7 and 9).

As shown in table III, we do not observe any noticeable difference in the reaction of 1,4-bis(bromomagnesio)pentane with N-substituted isatoic anhydrides (19-23). The desired 1,2-disubstituted 1-(o-aminophenyl)-2-methyl-cyclopentanols (24-28) are generated with a similar diastereoisomer distribution. In each case, the **trans**-OH isomer is the major reaction product. However, the substituent R on the nitrogen atom does not seem to particularly affect the diastereoselection. Furthermore, in attempt to separate the dia-

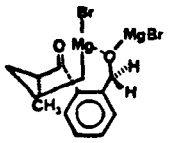


Figure 1

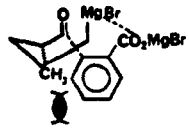


Figure 2

stereoisomers, we converted the 1-(o-aminophenyl)cyclopentanols (25-28) into the corresponding spiro compounds (29-32) by using n-butyllithium and diethyl carbonate (table III). However it has been difficult to achieve the separation of the isomers. The results reveal that, after cyclization, ^{1}H NMR chemical shifts data of the methyl groups of **trans** isomers similar to the spirolactone (8b) and have higher values than those of 1-substituted-2-methylcyclopentanols (2b), (24b-28b). In Table IV, we gathered results of ^{13}C NMR chemical shifts of compounds (24-28) and (29-32). Pertinent ^{13}C NMR shifts of methyl and carbinol carbons (c-1) allow determination, without ambiguity the **cis** or **trans** configuration.

In all cases, both methyl and carbinol carbon signals of **trans** isomers show higher values than those of **cis** isomers. Moreover, we can observe some differences between chemical shifts of cycloalkyl carbons (C-2, C-3, C-4, C-5).

Since all other factors were identical in these experiments, it became apparent that steric interactions influence the stereochemical course of the cyclization step rather than the difference of relative reactivity of the primary-secondary bis Grignard reagent.

Whatever the nature of substrates, the transition state of this cyclization leading mainly to the **trans** or the **cis** isomer, was due to the attack of the secondary function of the 1,4-bis(bromomagnesio)pentane (intermediate 1, scheme 1). The stereochemistry particularly depends on the steric effect of substrate rather than the bis Grignard reagent (Figure 1 and 2). Consequently, isomer distribution is evidence of structural geometric requirements for the annelation step where chelation of oxygen to magnesium occurs.

Experimental Section

Melting points were determined in capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Analytical thin-layer chromatography was performed on Woelm Silica Gel 60F 254 plates (0.25 mm). Purification and separation of products were achieved with ethyl acetate-petroleum ether (0 to 5% gradient) as the eluant. Infrared spectra were obtained on a Beckman IR-425 spectrophotometer. ^{1}H NMR spectra were determined on a Bruker HX-90 or on a Varian XL-200 spectrometer in $CDCl_3$ solution and are reported in δ units downfield from Me_4Si. ^{13}C NMR spectra were determined on a Bruker WP-80 or on a Varian XL-200 in $CDCl_3$ by using Me_4Si as internal standard. Mass spectra were obtained with a Hewlett-Packard 5995A GC/MS.

Starting Materials

All glassware used in these experiments was flamed out in a stream of dry nitrogen before use. A positive pressure of nitrogen was kept above solutions at all times. All reactions were carried out in a two-necked, 200 mL, round-bottomed flask, with a pressure-equalizing funnel, a water-cooled reflux condenser, and a Teflon-coated magnetic stirring bar. Tetrahydrofuran was distilled from lithium aluminium hydride into an ovendried flask and kept over sodium wire. 1,4-dibromopentane and all starting compounds were commercially available except in the case of N-ethylisatoic anhydride 21 and N-benzylisatoic anhydride 23[11], N-propylisatoic anhydride 22.

N-propylisatoic anhydride 22

This anhydride was prepared according to Hartmann[12] from isatoic anhydride and propyl bromide and recrystallized as light brown powder from methylene chloride-hexane, m.p. 94-95 °C; 45% yield; ^{1}H NMR δ 0.99-1.06 (t, 3H), 1.70-1.80 (m, 2H); 3.90-4.00 (m, 2H), 7.10-7.30 (m, 1H), 7.70-8.10 (m, 1H), 8.10-8.20 (m, 1H); ^{13}C NMR δ 147.00, 141.20, 137.10, 130.73, 123.73 (2C), 113.82, 111.62, 46.39, 20.23, 11.03.

Preparation of 1,4-Bis(bromomagnesio)pentane

In a typical reaction, 33 mmol of magnesium turnings was introduced in the system described above and was flame heated under nitrogen. The magnesium was covered by 5 ml of anhydrous THF, and a solution of 15 mmol of dibromide in 30 ml of THF was added dropwise at room temperature at such a rate that the temperature did not rise above 30°C. The reaction mixture was stirred for 2-4 h. Titration of bis Grignard reagent followed the procedure of Watson and Eastham[13].

Preparation of 1-(O-Hydroxymethylphenyl)-2-Methyl-cyclopentanols 2a,b

A solution of phthalide 1 (5.5 mmol) in 20 ml of anhydrous THF was added with stirring under nitrogen to 11 mmol of 1,4-bis(bromomagnesio)pentane prepared in the same solvent (30 ml). The reaction mixture was stirred for 1 h under an atmosphere of nitrogen. After hydrolysis with ammonium chloride, the organic layer was separated. The aqueous layer was extracted with ether and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated in vacuo and the residue was separated by flash chromatography, eluting with petroleum ether-ethyl acetate (9:1).

1-(O-Hydroxymethylphenyl)-2-methylcyclopentanols 2a,b

^{1}H NMR analysis revealed that 1-(o-hydroxymethylphenyl)-t-2-methylcyclopentan-r-1-ol(2b) was the major isomer (82%). The overall yield was 85%. The major product was purified by flash chromatography.

1-(O-Hydroxymethylphenyl)-t-2-methylcyclopentan-r-1-ol (2b)

Recrystallized as white powder from n-pentane, m.p. 84-86°C; ^{1}H NMR δ 0.48 (d, 3H, J = 7.3 Hz), 1.25-1.50 (m, 1H), 1.70-2.05 (m, 3H), 2.10-2.70 (m, 3H), 3.95 (s, 1H), 4.50 (s, 1H), 4.64 (q, 2H), 7.15-7.45 (m, 4H); ^{13}C NMR δ 142.52, 139.13, 131.44, 127.64, 127.59, 127.30, 87.40, 65.30, 41.29, 36.65, 31.81, 20.34, 19.95; IR (KBr) 3180, 3010, 2990, 2860, 1600, 1465, 1450, 1100, 1000, 738 cm^{-1}; mass spectrum, m/e (relative intensity) 207.2 (M^+,1.8), 206.3 (M^+,8.9), 183 (M^+-H_2O, 15.7), 155.2 (20.0), 145.3 (100), 135.2 (23.4), 131.2 (24.7), 119.2 (30.8), 118.2 (25.9), 115.1 (22.5), 91.20 (23.6), 90.20 (16.4), 77.2 (20.10). Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.62; H, 8.77.

1-(O-Hydroxymethylphenyl)-c-2-methylcyclopentan-r-1-ol (2a)

Viscous colorless liquid; ^{1}H NMR δ 0.96 (d, 3H, J = 6.66 Hz), 1.45-2.05 (m, 5H), 2.15-2.52

(m, 2H), 3.7-4.4 (s, 2H), 4.71 (q, 2H), 7.1-7.4 (m, 4H); ^{13}C NMR δ 142.25, 139.27, 131.25, 127.25, 127.07, 126.79, 87.35, 65.14, 43.93, 42.15, 31.24, 21.27, 12.70; IR (film) 3330, 3090, 3050, 3010, 2945, 2860, 1590, 1475, 1440, 1000, 748 cm^{-1}; mass spectrum, m/e (relative intensity) 207.4 (M^+,1.7), 206.3 (M^+, 10.4), 188.3 (M^+-H_2O,12.7), 146.3 (17.7), 145.3 (100), 135.2 (18.8), 132.2 (14.7), 131.2 (19.2), 119.2 (32.9), 118.2 (20.8), 115.2 (16.2), 91.2 (20.4), 90.2 (14.7), 77.2 (16.7). Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.62; H, 8.77.

Preparation of 1-(2-Hydroxystyryl)-2-Methylcyclopentanols 5,6

A solution of 15.3 mmol of coumarin 3, 4 in anhydrous THF (50 ml) was added with stirring under nitrogen to 15.3 mmol of 1,4-bis(bromomagnesio)pentane prepared in the same solvent (~50 ml). The reaction mixture was stirred for 1 h under an atmosphere of nitrogen. After hydrolysis with ammonium chloride, the organic layer was separated, the aqueous layer was extracted with ether, and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated in vacuo and the residue was separated by flash chromatography, eluting with petroleum ether-ethyl acetate (9:1).

1-(2-Hydroxystyryl)-2-Methylcyclopentanols 5 a,b

^{1}H NMR analysis revealed that 1-(2-hydroxystyryl)-t-2-methylcyclopentan-r-1-ol (5b) was the major isomer (70%). The overall yield was 55%. The diastereoisomers were purified by flash chromatography.

1-(2-Hydroxystyryl)-t-2-Methylcyclopentan-r-1-ol (5b)

White powder, m.p. 99-100 °C; ^{1}H NMR δ 0.87-0.90 (d, 3H, J=6.96 Hz), 0.93-2.05 (7m, 7H), 5.94-5.99 (d, 1H, J=12.5 Hz), 6.39-6.46 (d, 1H, J=12.5 Hz), 6.84-7.25 (m, 4H); ^{13}C NMR δ 152.51, 136.12, 129.64, 128.71, 125.41, 125.30, 120.28, 116.91, 84.26, 45.49, 37.96, 31.25, 20.65, 17.05; IR (nujol) 3570, 3310, 3160, 2940, 2860 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.90; H, 8.42.

1-(2-Hydroxystyryl-c-2-Methylcyclopentan-r-1-ol (5a)

White powder, m.p. 97-98 °C; ^{1}H NMR δ 0.94-0.98 (d, 3H, J=6.59 Hz), 1.00-1.86 (m, 7H), 5.32-5.82 (d, 1H, J=12.5 Hz), 6.38-6.44 (d, 1H, J=12.45 Hz), 6.82-7.16 (m, 2H); ^{13}C NMR δ 152.38, 138.36, 129.75, 128.66, 124.93 (2c), 120.18, 116.66, 83.17, 45.04, 39.58, 30.96, 21.45, 12.21; IR (nujol) 3570, 3310, 3160, 2940, 2860 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.90; H, 8.42.

1-(2-Hydroxy-5-Methylstyryl)-2-Methylcyclopentanols (6a,b)

^{1}H NMR analysis revealed that 1-(2-Hydroxy-5-methylstyryl)-t-2-methylcyclopentan-r-1-ol (6b) was the major isomer (68%). The overall yield was 60%. The diastereoisomers were purified by flash chromatography.

1-(2-Hydroxy-5-Methylstyryl-t-2-Methylcyclopentan-r-1-ol (6b)

White powder, m.p. 75-76°C; ^{1}H NMR δ 0.88-0.91 (d, 3H, J = 7.42 Hz), 1.20-1.38 (m, 1H), 1.65-1.98 (m, 6H), 2.25 (s, 3H), 5.91-5.98 (d, 1H, J = 8.5 Hz), 6.36-6.43 (d, 1H, J = 12.5 Hz), 6.75-6.95 (m, 3H); ^{13}C NMR δ 150.19, 135.88, 129.92, 129.41, 129.30, 125.51, 125.04, 116.82, 84.22, 45.55, 37.91, 31.25, 20.67, 20.54, 17.05; IR (nujol) 3260, 3100, 2900, 2840, 1450 cm^{-1}. Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.40; H, 8.64.

1-(2-Hydroxy-5-Methylstyryl)-c-2-Methylcyclopentan-r-1-ol (6a)

White powder, m.p. 104-105°C; ^{1}H NMR δ 0.95-0.98 (d, 3H, J = 7.42 Hz), 1.17-1.91 (m, 7H), 2.25 (s, 3H), 5.82-5.88 (d, 1H, J = 12.5 Hz), 6.36-6.42 (d, 1H, J = 12.5 Hz), 6.78-7.00 (m, 3H); ^{13}C NMR δ 150.00, 138.54, 129.35, 128.39, 127.13, 124.86, 121.51, 115.56, 83.08, 45.06, 39.53, 32.87, 21.61, 21.50, 12.17; IR (nujol) 3310, 2940, 2840, 1490 cm^{-1}. Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.40; H, 8.64.

Preparation of Spirolactones 8, 10, 12, 14, 16, 18. General Method

A solution of 12.7 mmol of cyclic anhydride 7, 9, 11, 13, 15, 17, in 100 ml of anhydrous THF was added with stirring under nitrogen to 12.7 mmol of 1,4-bis(bromomagnesio)pentane prepared in the same solvent (30 ml). The reaction mixture was stirred for an additional 4 h under an atmosphere of nitrogen. Then, the reaction mixture was hydrolyzed with 10% HCl and flame heated for 2 h. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried over anhydrous magnesium sulfate and the solution was concentrated in vacuo. The products were purified by flash chromatography. The diastereoisomeric spirolactones could have not been separated. Diastereoisomer distribution was determined by ^{1}H NMR spectroscopy.

Spiro[2-methylcyclopentane-1,1'-3H-isobenzofuran]-3'-ones (8a,b)

^{1}H NMR analysis revealed that the cis isomer (8a) was the major product (100%). The overall yield was 70%. The **cis** isomer was isolated by flash chromatography. The **trans** isomer (8b)

could have not been obtained by the reaction of phthalic anhydride with 1,4-bis(bromomagnesio)pentane but, was prepared by oxidation of the cyclopentanol) (2b).

c-Spiro[2-methylcyclopentane-1, 1'-3H-isobenzofuran]-3'-one (8a)

Recrystallized as white powder from n-pentane-petroleum ether, m.p. 75-77°C; ^{1}H NMR δ 0.72 (d, 3H, J = 6.59 Hz), 1.50-2.50 (m, 7H), 7.30-8.00 (m, 4H); ^{13}C NMR δ 170.15, 151.06, 133.99, 128.70, 125.18, 125.02, 120.70, 96.49, 44.93, 38.61, 32.28, 22.04, 11.31; IR (KBr) 3100, 3000, 2950, 2925, 2870, 1765, 1640, 1555, 1100, 1000 cm^{-1}. Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.17; H, 6.93.

t-Spiro[2-methylcyclopentane,1,1'-3H-isobenzofuran]-3'-one (8b)

White powder; ^{1}H NMR δ 0.57-0.60 (d, 3H, J=6.60 Hz), 1.40-2.40 (m, 6H), 7.30-7.80 (m, 4H); ^{13}C NMR δ 169.30, 150.41, 133.20, 128.38, 124.88, 122.24, 120.25, 96.46, 43.69, 36.71, 32.31, 21.36, 15.61; IR (KBr) 3100, 3000, 2850, 1755, 1080 cm^{-1}. Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.15; H, 6.91.

Spiro[2-methylcyclopentane-1,1'-3H-isonaphthofuran]-3'-ones (18a,b)

^{1}H NMR analysis revealed that only the cis isomer (10a) was isolated (100%). The overall yield was 65%. The cis isomer was purified by flash chromatography.

c-Spiro[2-methylcyclopentane-1,1'-3H-isonaphthofuran]-3'-one (18a)

Recrystallized as yellow powder from n-pentane-petroleum ether, m.p. 99-101°C; ^{1}H NMR δ 0.73 (d, 3H, J = 6.50 Hz), 1.55-2.66 (m, 7H), 7.2-8.5 (m, 6H); ^{13}C NMR δ 169.90, 145.75, 139.10, 136.68, 133.54, 128.93, 128.34, 126.88, 126.67, 125.27, 119.71, 96.88, 46.24, 39.88, 32.71, 22.46, 11.78; IR (KBr) 3050, 2950, 2925, 2870, 1765, 1640, 1470, 1455 cm^{-1}. Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.88; H, 6.35.

Spiro-[2-methylcyclopentane-1,1'-bicyclo[3.2.0]heptan]-3'-ones (12a,b)

^{1}H NMR analysis revealed that the trans isomer (12b) was the major product (67%). The overall yield was 69%. The mixture of diastereoisomers was purified by flash chromatography.

t-Spiro[2-methylcyclopentane-1,1'-bicyclo[3.2.0]heptan]-3'-one (12b)

Colorless liquid, distillation bp 108.109°C (1mmHg); ^{1}H NMR δ 0.88 (d, 3H, J = 7.04 Hz), 1.3-3.3 (m, 26H); ^{13}C NMR δ 180.45, 97.39, 43.17, 41.27, 39.29, 35.93, 31.68, 22.97, 21.73, 20.71, 16.68; IR (film) 2950, 2870, 1770, 1455, 1378 cm^{-1}. Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.23; H, 8.91.

c-Spiro[2-methylcyclopentane-1,1'bicyclo[3.2.0]heptan]-3'-one (12a)

Colorless liquid, distillation bp 108-109°C (1mmHg); ^{1}H NMR δ 0.91 (d, 3H, J = 6.75 Hz), 1.3-3.3 (m, 26 H); ^{13}C NMR δ 180.51, 100.10, 45.66, 41.64, 40.83, 38.05, 31.90, 22.61, 22.24, 21.29, 12.36; IR (film) 2950, 2870, 1770, 1455, 1378 cm^{-1}. Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30, H, 8.95. Found: H, 8.91.

Tetrahedro-4',5',6',7'-spiro[2-methylcyclopentane-1,1'-3H-isobenzofuran]-3'-ones (14a,b)

^{1}H NMR analysis revealed that the trans isomer (14b) was the major product (67%). The overall yield was 64%. The mixture of diastereoisomers was purified by flash chromatography.

t-Tetrahedro-4',5',6',7'-spiro[2-methylcyclopentane-1,1'-3H-isobenzofuran]-3'-one (14b)

White powder; ^{1}H NMR δ 0.96 (d, 3H, J = 7.5 Hz), 1.25-3.25 (m, 28H), 5.92 (m, 4H); ^{13}C NMR δ 178.32, 125.27, 124.75, 99.22, 42.00, 39.80, 38.63, 35.19, 31.97, 22.90, 22.24, 20.78, 17.71; IR (KBr) 3030, 2960, 2840, 1775 cm^{-1}; mass spectrum, m/e (relative intensity) 206.0 (M$^+$, 10.3), 163.1 (27.7), 108.1 (35.6), 107.0 (25.2), 91.1 (27.1), 80.1 (40.5), 79.0 (100), 77.1 (52.5), 41.1 (44.1). Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.73; H, 8.77. Found: C, 75.64; H, 8.72.

c-Tetrahedro-4',5',6',7'-spiro[2-methylcyclopentane-1,1'-3H-isobenzofuran]-3'-one (14a)

White powder; ^{1}H NMR δ 1.14 (d, 3H, J = 7.0 Hz), 1.25-3.25 (m, 28H), 5.92 (m, 4H); ^{13}C NMR δ 179.19, 125.93, 125.49, 99.51, 42.95, 41.34, 39.80, 38.63, 32.19, 22.54, 22.24, 21.66, 13.39; IR (KBr) 3030, 2960, 2840, 1775 cm^{-1}; mass spectrum, m/e (relative intensity) 206.0 (M$^+$, 10.3), 163.1 (27.7), 108.1 (35.6), 107.0 (25.2), 91.1 (27.1), 80.1 (40.5), 79.0 (100), 77.1 (52.5), 41.1 (44.1). Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.73; H, 8.77. Found: C, 75.64; H, 8.72.

2-Methyl-2'-oxaspiro[4.5]decan-3'-one (16a,b)

^{1}H NMR analysis revealed that the trans isomer (16b) was the major product and constituted 85% of the mixture of the spirolactones. The overall yield was 38%. The mixture of diastereoisomers was purified by flash chromatography.

2-Methyl-t-2'-oxaspiro[4.5]decan-3'-one (16b)

^{1}H NMR δ 0.91 (d, 3H, J=7.33 Hz), 1.20-2.60 (m, 13H), ^{13}C NMR δ 171.79, 95.06, 60.13, 43.33, 43.33, 36.60, 31.47, 29.54, 20.81, 16.06; IR (film) 2875-2830, 1730, 1455, 1375, 1250 cm^1; mass spectrum, m/e (relative intensity) 169 (M^{+1}, 3%), 168 (M, 31%), 112(66%), 97(57%),

85(75%), 84(47%), 83(56%), 81(45%), 58(47%), 55(100%). Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.92; H, 9.41.

2-Methyl-c-2'-oxaspiro[4.5]decan-3'-one (16a)

^{1}H NMR δ 1.00 (d, 3H, J=6.22 Hz), 1.20-2.60 (m, 13H); ^{13}C NMR δ 166.30, 94.74, 60.53, 44.13, 44.13, 39.31, 31.27, 29.72, 21.01, 13.00; IR (film) 2875-2830, 1730, 1455, 1375, 1250 cm^{-1}; mass spectrum, m/e (relative intensity) 169(M^{+1}, 3%), 168(M, 31%), 112(66%), 97(57%), 85(75%), 84(47%), 83(56%), 81(45%), 58(47%), 55(100%). Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.10; H, 9.43.

2,4',4'-Trimethyl-2-oxaspiro[4.5]decan-3'-one (18a,b)

^{1}H NMR analysis revealed that the **trans** isomer (18b) was the major product and constituted 77% of the mixture of the spirolactones. The overall yield was 62%. The mixture of diastereoisomers was purified by flash chromatography.

2,4',4'-Trimethyl-t-2'-oxaspiro[4.5]decan-3'-one (18b)

^{1}H NMR δ 0.89 (d, 3H, J=6.23 Hz), 1.09 (s, 3H), 1.12 (s, 3H), 1.00-2.00 (m, 7H), 1.60 (dd, 1H, J=14.28 Hz, J=1.47 Hz), 1.84 (d, 1H, J=14.28 Hz), 2.23 (d, 1H, J=16.48 Hz), 2.32 (d, 1H, J=16.48 Hz); ^{13}C NMR δ 171.81, 93.64, 51.35, 44.89, 43.84, 40.31, 38.15, 30.85, 30.85, 30.12, 20.56, 16.30; IR (film) 2940-2860, 1720, 1455, 1360, 1345, 1260 cm^{-1}; mass spectrum, m/e (relative intensity) 197 (M^+, 2%), 196 (M, 9%), 140(18%) 83(87%), 81(20%), 70(17%), 69(30%), 56(46%), 55(100%), 53(27%). Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.16.

2,4',4'-Trimethyl-c-2'-oxaspiro[4.5]decan-3'-one (18a)

^{1}H NMR δ 0.97 (d, 3H, J=6.23 Hz), 1.07 (s, 3H), 1.16 (s, 3H), 1.00-2.00 (m, 7H), 1.60 (dd, 1H, J=14.28 Hz, J=1.47 Hz), 1.84 (d, 1H, J=14.28 Hz), 2.23 (d, 1H, J=16.48 Hz), 2.32 (d, 1H, J=16.48 Hz); ^{13}C NMR δ 166.31, 92.08, 63.16, 44.78, 43.80, 41.75, 36.45, 31.29, 31.29, 29.83, 21.92, 12.08; IR (film) 2940-2860, 1720, 1455, 1360, 1345, 1260 cm^{-1}; mass spectrum, m/e (relative intensity) 197 (M^+, 2%), 196 (M, 9%), 140(18%), 83(87%), 81(20%), 70(17%), 69(30%), 56(46%), 55(100%), 53(27%). Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.40; H, 10.12.

Preparation of 1,2-Disubstituted 1-(o-Aminophenyl)-2-Methylcyclopentanols 24-28. General Method.

A solution of the anhydride 19-23 (15.3 mmol) in ~50 ml of anhydrous THF or diethylic ether was added to 15.3 mmol of 1,4-bis(bromomagnesio)pentane prepared in the same solvent (~50 ml). The reaction mixture was stirred for 1 h under an atmosphere of nitrogen. After hydrolysis with saturated ammonium chloride, the organic layer was separated, the aqueous layer was extracted with ether, and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was concentrated in vacuo and the residue was purified by column chromatography, eluting with petroleum ether-ethyl acetate (9:1-4:1). The separation of diastereoisomers was difficult to achieve. Elementary analysis were carried out on the crude reaction mixture and isomer distribution was determined by ^{1}H NMR spectroscopy.

1-(o-Aminophenyl)-2-methylcyclopentanols (24a,b)

^{1}H NMR analysis revealed that 1-(o-aminophenyl)-t-2-methylcyclopentan-r-1-ol(24b) was the major isomer (67%). The overall yield was 20%. The mixture of diastereoisomers was purified by flash chromatography.

1-(o-Aminophenyl)-t-2-methylcyclopentan-r-1-ol (24b)

Liquid; ^{1}H NMR δ 0.45-0.49 (d, 3H, J = 7.47 Hz), 1.14-1.95 (m, 6H), 233-2.46 (m, 1H), 3.77-4.05 (s, 3H), 6.55-6.64 (m, 2H), 6.93-7.07 (m, 2H); ^{13}C NMR δ 146.34, 134.45, 128.49, 127.91, 118.17, 117.82, 87.00, 42.24, 39.84, 31.79, 20.59, 19.83; IR (nujol) 3680, 3000 cm^{-1}; mass spectrum, m/e (relative intensity) 191 (M^+, 27%), 173 (M^+-H_2O, 25%), 120 (100%). Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.39; H, 8.90, N, 9.72. Found: C, 75.50; H, 8.78; N, 7.25.

1-(o-Aminophenyl)-c-2-methylcyclopentan-r-1-ol (24a)

^{1}H NMR δ 0.98-1.00 (d, 3H, J = 6.59 Hz), 1.14-1.95 (m, 6H), 2.33-2.46 (m, 1H), 3.77-4.05 (s, 3H), 6.55-6.64 (m, 2H), 6.93-7.07 (m, 2H); ^{13}C NMR δ 146.34, 134.38, 128.28, 127.37, 118.06, 117.64, 84.60, 41.24, 38.33, 31.18, 21.08, 13.01; IR (nujol) 3680, 3000 cm^{-1}; mass spectrum, m/e (relative intensity) 191 (M^+, 27%), 173 (M^+-H_2O, 25%), 120 (100%). Anal. for $C_{12}H_{17}NO$: C, 75.39; H, 8.90; N, 9.72. Found: C, 75.50; H, 8.78; N, 7.25.

1-(o-Methylaminophenyl)-2-methylcyclopentanols (25a,b)

^{1}H NMR analysis revealed that 1-(o-methylaminophenyl)-t-2-methylcyclopentan-r-1-ol (25b) was the major isomer (67%). The overall yield was 70%. The mixture of diastereoisomers was purified by flash chromatography.

1-(o-Methylaminophenyl)-t-2-methylcyclopentan-r-1-ol (25b)

Liquid; ^{1}H NMR δ 0.39-0.43 (d, 3H, *J* = 7.30 Hz), 1.66-2.70 (m, 7H), 2.71 (s, 3H), 3.10-3.90 (s, 2H), 6.51-6.57 (m, 2H), 7.00-7.09 (m, 2H); ^{13}C NMR δ 149.36, 128.24, 127.19, 125.15, 115.58, 110.89, 87.59, 40.98, 38.24, 31.83, 30.54, 21.07, 19.96; IR (nujol) 3520, 3400 cm^{-1}; mass spectrum, m/e (relative intensity) 205 (M^+, 17%), 187 (M^+-H_2O, 11%), 130 (100%). Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.09; H, 9.27; N, 6.83. Found: C, 76.19; H, 9.32; N, 6.69.

1-(o-Methylaminophenyl)-c-2-methylcyclopentan-r-1-ol (25a)

^{1}H NMR δ 0.95-0.98 (d, 3H, *J* = 6.67 Hz), 1.66-2.70 (m, 7H), 2.71 (s, 3H), 3.10-3.90 (s, 2H), 6.51-6.57 (m, 2H), 7.00-7.09 (m, 2H); ^{13}C NMR δ 148.91, 128.55, 127.84, 126.33, 115.42, 110.34, 84.75, 39.51, 36.65, 31.18, 30.54, 20.59, 13.08; IR (nujol) 3520, 3400 cm^{-1}; mass spectrum, m/e (relative intensity) 205 (M^+, 17%), 187 (M^+-H_2O, 11%), 130 (100%). Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.09; H, 9.27; N, 6.83. Found: C, 76.19; H, 9.32; N, 6.69.

1-(o-Ethylaminophenyl)-2-methylcyclopentanols (26a,b)

^{1}H NMR analysis revealed that 1-(o-ethylaminophenyl)-t-2-methylcyclopentan-r-1-ol (26b) was the major isomer (65%). The overall yield was 65%. The mixture of diastereoisomers was purified by flash chromatography.

1-(o-Ethylaminophenyl)-t-2-methylcyclopentan-r-1-ol (26b)

Liquid; ^{1}H NMR δ 0.49-0.53 (d, 3H, *J* = 7.31 Hz), 1.22-1.86 (m, 12H), 3.09-3.16 (m, 2H), 6.58-6.70 (m, 2H), 7.02-7.23 (m, 2H); ^{13}C NMR δ 148.02, 128.24, 127.82, 126.50, 115.58, 110.91, 87.60, 41.08, 38.31, 36.82, 31.91, 20.70, 20.08, 14.91; IR (nujol) 3520, 3390 cm^{-1}; mass spectrum, m/e (relative intensity) 219 (M^+, 44%), 201 (M^+-H_2O, 10%), 148 (100%). Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.71; H, 9.59; N, 6.39. Found: C, 76.17; H, 9.61; N, 6.41.

1-(o-Ethylaminophenyl)-c-2-methylcyclopentan-r-1-ol (26a)

^{1}H NMR δ 1.05-1.08 (d, 3H, *J* = 6.67 Hz), 1.22-1.86 (m, 12H), 3.09-3.16 (m, 2H), 6.58-6.67 (m, 2H), 7.02-7.23 (m, 2H); ^{13}C NMR δ 148.51, 128.55, 127.08, 125.30, 115.36, 111.53, 84.80, 39.58, 38.38, 38.18, 31.93, 21.14, 14.14, 13.14; IR (nujol) 3520, 3390 cm^{-1}; mass spectrum, m/e (relative intensity) 219 (M^+, 44%), 201 (M^+-H_2O, 10%), 148 (100%). Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.71; H, 9.59; N, 6.39. Found: C, 76.17; H, 9.61; N, 6.41.

1-(o-Propylaminophenyl)-2-methylcyclopentanols (27a,b)

^{1}H NMR analysis revealed that 1-(o-propylaminophenyl)-t-2-methylcyclopentan-r-1-ol (27b) was the major isomer (80%). The overall yield was 54%. The mixture of diastereoisomers was purified by flash chromatography.

1-(o-Propylaminophenyl)-t-2-methylcyclopentan-r-1-ol (27b)

Liquid; ^{1}H NMR δ 0.39-0.43 (d, 3H, *J* = 7.33 Hz), 1.14-2.60 (m, 11H), 2.89-3.03 (m, 2H), 6.44-6.56 (m, 2H), 6.92-7.09 (m, 2H); ^{13}C NMR δ 148.02, 128.44, 127.72, 126.41, 115.15, 110.67, 87.51, 45.51, 39.57, 36.69, 31.93, 22.59, 20.68, 20.01, 11.95; IR (nujol) 3520, 3390 cm^{-1}; mass spectrum, m/e (relative intensity) 233 (M^+, 40%), 217 (M^+-H_2O, 18%), 162 (100%). Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.25; H, 9.87; N, 6.00. Found: C, 76.43; H, 9.38; N, 5.73.

1-(o-Propylaminophenyl)-c-2-methylcyclopentan-r-1-ol (27a)

^{1}H NMR δ 0.84-1.10 (d, 3H, *J* = 6.67 Hz), 1.14-2.60 (m, 11H), 2.89-3.03 (m, 2H), 6.44-6.56 (m, 2H), 6.92-7.09 (m, 2H); ^{13}C NMR δ 148.88, 128.15, 127.00, 125.22, 115.38, 111.33, 84.73, 45.62, 41.02, 38.07, 31.25, 21.10, 20.01, 13.09, 11.95; IR (nujol) 3520, 3340 cm^{-1}; mass spectrum, m/e (relative intensity) 233 (M^+, 40%), 217 (M^+-H_2O, 18%), 162 (100%). Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.25; H, 9.87; N, 6.00. Found: C, 76.43; H, 9.78; N, 5.73.

1-(o-Benzylaminophenyl)-2-methylcyclopentanols (28a,b)

^{1}H NMR δ analysis revealed that 1-(o-benzylaminophenyl)-t-2-methylcyclopentan-r-1-ol (28b) was the major isomer (60%). The overall yield was 52%. The mixture of diastereoisomers was purified by flash chromatography.

1-(o-Benzylaminophenyl)-t-2-methylcyclopentan-r-1-ol (28b)

Liquid; ^{1}H NMR δ 0.54-0.58 (d, 3H, *J* = 7.30 Hz), 1.19-2.90 (m, 9H), 4.32 (s, 2H), 6.56-6.65 (m, 2H), 7.07-7.39 (m, 2H); ^{13}C NMR δ 148.10, 139.79, 128.43, 128.38, 127.99, 127.36, 127.09, 126.98, 126.75, 126.47, 115.78, 111.18, 87.54, 47.80, 39.49, 36.57, 31.79, 21.01, 20.56; IR (nujol) 3520, 3390, 3080, 3020, 2940, 2860 cm^{-1}; mass spectrum, m/e (relative intensity) 281 (M^+, 17%), 268 (M^+-H_2O, 13%), 91 (100%). Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.14; H, 8.19; N, 4.98. Found: C, 81.99; H, 8.13; N, 4.63.

1-(o-Benzylaminophenyl)-c-2-methylcyclopentan-r-1-ol (28a)

^{1}H NMR δ 1.05-1.08 (d, 3H, *J* = 6.67 Hz), 1.19-2.90 (m, 9H), 4.32 (s, 2H), 6.56-6.65 (m, 2H), 7.04-7.39 (m, 2H); ^{13}C NMR δ 147.56, 139.72, 128.53, 128.23, 127.70, 127.24, 127.16, 126.92, 126.78, 125.27, 115.91, 111.66, 84.74, 47.88, 39.23, 38.26, 31.16, 19.95, 13.01; IR (nujol) 3520, 3390, 3080, 3020, 2940, 2860 cm^{-1}; mass spectrum, m/e (relative intensity) 281 (M^+,

17%), 268 (M^+-H_2O), 13%), 91 (100%). Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.14; H, 8.19; N, 4.98. Found: C, 81.99; H, 8.13; N, 4.63.

Preparation of Spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'-ones 29-32. General Method.

The 1-(o-Aminophenyl)cyclopentanols **25-28 (a,b)** obtained from isatoic anhydrides **19-23** (11 mmol) in anhydrous THF (50 ml) were cooled to 0 °C with an ice bath under an atmosphere of nitrogen and then, 11 mmol of n-butyllithium (1.55 M in hexane was added dropwise to the solution and stirred for 30 min at the same temperature and for an additional 3 h at room temperature. After hydrolysis with ammonium chloride, the organic layer was separated, the aqueous layer was extracted with ether and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the resulting residue was separated by column chromatography, eluting with petroleum ether (40-60 °C).
ethyl acetate (9:1-5:1).

N-Methyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin] (29a,b)

^{1}H NMR analysis revealed that t-N-methyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'-one (29b) was the major isomer (67%). The overall yield was 85%.

t-N-Methyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'one (29b)

Liquid; ^{1}H NMR δ 0.54-0.57 (d, 3H, J = 6.98 Hz), 1.22-2.52 (m, 7H), 3.37-3.38 (s, 3H), 6.93-7.40 (m, 4H); ^{13}C NMR δ 152.35, 137.33, 128.44, 124.17, 124.05, 122.16, 112.54, 92.82, 42.17, 39.49, 30.37, 30.29, 20.46, 16.97; IR (nujol) 1715 cm^{-1}; mass spectrum, m/e (relative intensity) 231 (M^+, 10%), 187 (M^+-CO_2, 29%), 130 (100%). Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.72; H, 7.36; N, 6.06. Found: C, 72.38; H, 7.37; N, 5.95.

c-N-Methyl-spiro[2-methylcyclopentane-1,4'2H-3',1'-benzoxazin]-2'-one (29a)

^{1}H NMR δ 0.98-1.02 (d, 3H, J = 6.67 Hz), 1.22-2.52 (m, 7H), 3.37-3.88 (s, 3H), 6.93-7.40 (m, 4H); ^{13}C NMR δ 152.08, 137.62, 128.26, 124.63, 122.68, 122.64, 112.70, 91.56, 43.81, 39.41, 31.44, 30.29, 20.55, 11.86; IR (nujol) 1715 cm^{-1}; mass spectrum, m/e (relative intensity) 231 (M^+, 10%), 187 (M^+-CO_2, 29%), 130 (100%). Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.72, H, 7.36; N, 6.06. Found: C, 72.38; H, 7.37; N, 5.95.

N-Ethyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'ones (30a,b)

^{1}H NMR analysis revealed that t-N-ethyl-spiro[2-methylcyclopentane-1,4'-2H-3'1'-benzoxazin]-2'-one (30b) was the major isomer (67%). The overall yield was 65%.

t-N-Ethyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'one (30b)

Liquid; ^{1}H NMR δ 0.54-0.57 (d, 3H, J = 7.30 Hz), 1.27-1.39 (t, 3H), 1.74-2.06 (m, 4H), 2.27-2.40 (m, 3H), 3.92-4.04 (q, 2H), 6.94-7.34 (m, 4H); ^{13}C NMR δ 151.95, 136.89, 128.42, 124.57, 122.97, 122.19, 112.96, 92.79, 42.80, 39.91, 38.84, 31.91, 30.71, 20.98, 17.28; IR (nujol) 1705 cm^{+1}; mass spectrum, m/e (relative intensity) 245 (M^+, 10%), 201 (M^+-CO_2, 10%). Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.46; H, 7.75; N, 5.71. Found: C, 73.12; H, 7.80; N, 5.48.

c-N-Ethyl-spiro[2-methylcyclopentane-1,4'-2H-3'1'-benzoxazin]-2'-one (30a)

^{1}H NMR δ 0.98-1.02 (d, 3H, J = 6.66 Hz), 1.27-1.39 (t, 3H), 1.74-2.06 (m, 4H), 2.27-2.40 (m, 3H), 3.92-4.04 (q, 2H), 6.94-7.34 (m, 4H); ^{13}C NMR δ 150.08, 137.37, 128.59, 124.82, 123.22, 122.69, 112.87, 91.66, 44.59, 39.91, 38.78, 35.16, 30.71, 20.98, 12.26; IR (nujol) 1705 cm^{-1}; mass spectrum, m/e (relative intensity) 245 (M^+, 10%), 201 (M^+-CO_2, 10%). Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.46; H, 7.75; N, 5.71. Found: C, 73.12; H, 7.80; N, 5.48.

N-Propyl-spiro[2-methylcyclopentane-1,4'-2H-3,1'-benzoxazin]-2'-ones (31a,b)

GLC analysis revealed that t-N-propyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'-one (31b) was the major isomer (58%). The overall yield was 62%.

t-N-Propyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'-one (31b)

Liquid; ^{1}H NMR δ 0.54-0.57 (d, 3H, J = 7.00 Hz), 1.20-2.46 (m, 9H), 3.80-3.91 (m, 2H), 6.90-6.96 (m, 1H), 7.02-7.16 (m, 2H), 7.25-7.32 (m, 1H); ^{13}C NMR δ 150.51, 136.59, 128.39, 125.28, 124.60, 122.22, 113.16, 92.86, 45.35, 42.77, 31.98, 30.73, 21.03, 20.12, 17.43, 11.22 ($CH_2\underline{CH_3}$); IR (nujol) 1705 cm^{-1}. Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.02; H, 8.44; N, 5.09.

c-N-Propyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'-one (31a)

^{1}H NMR δ 0.95-1.03 (d, 3H, J = 6.70 Hz), 1.20-2.46 (m, 9H), 3.80-3.91 (m, 2H), 6.90-6.97 (m, 1H), 7.02-7.16 (m, 2H), 7.25-7.32 (m, 1H); ^{13}C NMR δ 150.09, 136.42, 128.57, 125.08, 123.24, 122.69, 113.09, 91.90, 44.55, 40.04, 35.18, 30.73, 21.03, 20.12, 12.32, 11.22; IR (nujol) 1705 cm^{-1}. Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.13; H, 8.11; N, 5.41. Found: C, 74.02; H, 8.44; N, 5.09.

N-Benzyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'benzoxazin]-2'-ones (32a,b)
^{1}H NMR analysis revealed that t-N-benzyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'-one (32b) was the major isomer (60%). The overall yield 51%.
t-N-Benzyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'-one (32b)
Liquid; ^{1}H NMR δ 0.54-0.58 (d, 3H, J = 6.96 Hz), 1.26-2.54 (m, 7H), 5.04-5.23 (s, 2H), 6.80-7.41 (m, 9H); ^{13}C NMR δ 150.69, 136.28, 128.66(d), 128.59, 127.17(d), 126.42(d), 124.50, 123.15, 122.53, 114.11, 92.33, 47.82, 42.93, 40.40, 30.82, 21.16, 17.54; IR (nujol) 1700 cm^{-1}. Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.18; H, 6.84; N, 4.56. Found: C, 77.96; H, 6.79; N, 4.48.
c-N-Benzyl-spiro[2-methylcyclopentane-1,4'-2H-3',1'-benzoxazin]-2'-one (32a)
^{1}H NMR δ 1.03-1.07 (d, 3H, J = 6.97 Hz), 1.26-1.54 (m, 7H), 5.04-5.23 (s, 2H), 6.80-7.41 (m, 9H); ^{13}C NMR δ 150.37, 136.08, 128.66(d), 128.59, 127.17(d), 126.42(d), 124.40, 123.04, 122.53, 114.11, 93.48, 47.82, 44.73, 35.29, 32.07, 21.10, 12.43; IR (nujol) 1700 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.18; H, 6.84; N, 4.56. Found: C, 77.96; H, 6.84; N, 4.48.

Acknowledgment

We gratefully acknowledge financial support from the Natural Sciences and Engineering Research Council of Canada and the Fonds F.C.A.R. (Gouvernement du Québec).

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