Acknowledgment. We are grateful to The Robert A. Welch Foundation for support of this work.

William T. Brady,* Y. Frank Giang
Department of Chemistry
North Texas State University
Denton, Texas 76203
Received February 3, 1986

Reaction of 1,4-Bis(bromomagnesio)pentane and 1,5-Bis(bromomagnesio)hexane with Carboxylic Acid Esters. A Useful, Highly Stereoselective Annelation

Summary: 1,4-Bis(bromomagnesio)pentane and 1,5-bis(bromomagnesio)hexane have been prepared in TFH solution and, when treated with carboxylic acid esters, they afford trans diastereomeric bisubstituted cycloalkanols via a highly diastereoselective intramolecular Grignard reaction.

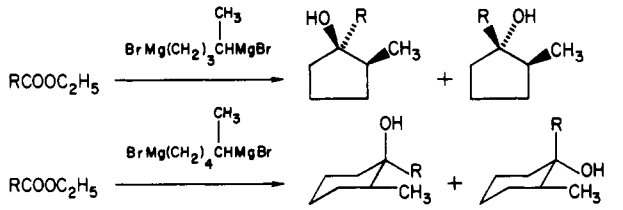
Sir: We have previously reported a versatile one-step synthesis leading to high yields of 1-substituted-cycloalkanols,[1] 1-(ω-hydroxyalkyl)cycloalkanols,[2] and spirolactones.[3] The crucial step is the reaction of α,ω-diprimary di-Grignard reagents with carboxylic acid esters, lactones, and cyclic anhydrides. The results lead to the conclusion that cyclization to a five or a six membered ring is favored over the many possible intra- and intermolecular reactions. Under normal dilution conditions, 1,4-bis(bromomagnesio)butane yields no product arising from intramolecular reduction or enolization when treated with hindered esters.[1] Experiments aimed at seven-membered ring diols[4] and spirolactones showed that dilution does not augment the yields which at best were very low.

The use of 1,3-bis(bromomagnesio)propane with the same series of cyclic anhydrides (mentioned above) gave the corresponding four-membered spirolactones[5] but in lower yields than those reported by Bickelhaupt for the reaction of this di-Grignard with carbon dioxide.[6]

Following our success with the diprimary reagents, we have now prepared some primary–secondary bis-Grignard reagents to follow their reactions with carboxylic acid derivatives particulary because this annelation should enable one to determine the factors which control diastereoselection in intramolecular Grignard reactions.

The primary–secondary bis-Grignards **1** and **2** were prepared from the readily available dibromides[7] in THF solution in yields of 80% and 85% by using the procedure established for the diprimary reagents. Treating these reagents with a series of carboxylic acid esters should reveal if the size of the ring being formed would influence the diastereomer distribution. (Scheme I). The results (Table I) show that the annelation is highly stereoselective affording preferentially the *trans*-2-methyl-1-substituted-cyclopentanols, but the structure of the starting ester has a striking effect on the reaction rate and the isomer distribution. The significance of these observations lies in the fact that the *trans*-OH diastereoisomers which are the major products cannot be obtained conveniently by other general routes.[8] The analysis of the diastereomeic products results from ^1H and ^{13}C NMR spectroscopy, gas chromatography, and high performance liquid chromatography. Published data for certain isomeric 2-methyl-1-substituted-cyclopentanols[9] and cyclohexanols[10] arising

Scheme I



Scheme II

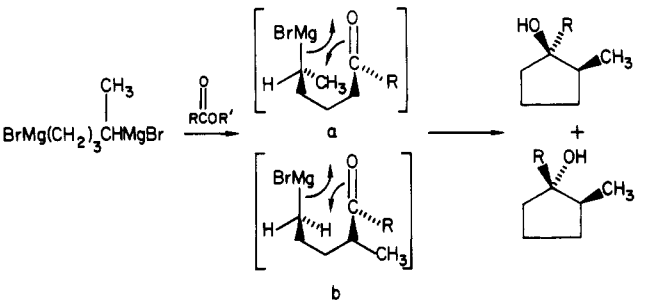


Table I. Reactions of 1,4-Bis(bromomagnesio)pentane with Carboxylic Acid Esters in THF Diastereoisomer Distribution

	2-methyl-1-substituted-cyclopentanols[a,b]		
ester, R	yield (%)	*cis*-OH	*trans*-OH
3, H	**12** 88	23	77
4, CH_3	**13** 77	6	94
5, CH_3CH_2	**14** 76	7	93
6, $C_6H_{11}CH_2$	**15** 81	6	94
7, C_6H_{11}	**16** 75	5	95
8, C_6H_5	**17** 78	11	89
9, *p*-$CH_3C_6H_4$	**18** 70	23	77
10, *p*-ClC_6H_4	**19** 74	18	82
11, *p*-$CH_3OC_6H_4$	**20** 75	40	60

[a] Isolated product. [b] Ratios of diastereomers determined by GC and ^1H NMR.

Table II. ^{13}C NMR Shifts of *cis,trans*-2-Methyl-1-substituted-cyclopentanols

	HO R, CH3		R OH, CH3	
R	δ(CH_3)	δ(C-1)	δ(CH_3)	δ(C-1)
H	13.68	76.02	18.29	80.41
CH_3	12.51	80.63	18.14	81.07
CH_3CH_2	12.59	82.31	16.54	84.22
$C_6H_{11}CH_2$	12.58	82.46	16.61	84.44
C_6H_{11}	12.58	84.29	17.49	87.00
C_6H_5	12.00	83.85	18.29	85.90
p-$CH_3C_6H_4$	12.07	83.34	18.36	85.75
p-ClC_6H_4	12.00	83.70	18.22	85.54
p-$CH_3OC_6H_4$	12.07	83.56	18.31	85.80

(1) (a) Canonne, P.; Bélanger, D.; Lemay, G. *Tetrahedron Lett.* **1981**, *22*, 4995. (b) Bélanger, D.; M.Sc. Thesis, Univesité Laval, 1979.
(2) Canonne, P.; Foscolos, G. B.; Bélanger, D. *J. Org. Chem.* **1980**, *45*, 1828.
(3) Canonne, P.; Bélanger, D.; Lemay, G.; Foscolos, G. B. *J. Org. Chem.* **1981**, *46*, 3091.
(4) Canonne, P.; Bélanger, D.; Lemay G. *Heterocycles* **1981**, *15*, 455.
(5) Canonne, P. unpublished results.
(6) Seetz, J. W. F. L.; Tol, R.; Akkerman, O. S.; Bickelhaupt, F. *Synthesis* **1983**, *9*, 721.
(7) Is obtained from commercially available 1,5-hexanediol by reaction with PBr_3. Kornblum, N.; Eicher, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2259.
(8) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

0022-3263/86/1951-2147$01.50/0

Table III. Reactions of 1,5-Bis(bromomagnesio)hexane with Carboxylic Acid Esters in THF Diastereoisomer Distribution

	2-methyl-1-substituted-cyclohexanols[a,b]		
ester, R	yield (%)	*cis*-OH	*trans*-OH
3, H	**21** 57	30	70
4, CH_3	**22** 53	25	75
8, C_6H_5	**23** 54	25	75

[a] Isolated product. [b] Ratios of diastereomers determined by GC and ^1H NMR.

from previous studies of organometallic reactions of 2-methyl-cycloalkanones greatly facilitated this aspect of the study. Pertinent ^{13}C NMR shifts of the methyl and the carbinol carbons, listed in Table II, show that this method readily distinguishes the cis from the trans isomers. The methyl carbon signals of the later consistently appear about 4 ppm downfield from those of the cis diastereoisomers. The carbinol carbon signals are less susceptible to changes in structure but in general the shifts for the cis cyclopentanols have lower values than the trans isomers. In the ^1H NMR spectra the protons of the methyl groups in the trans isomers invariably appear the further upfield, while the results of gas chromatography and flash chromatography show the cis-substituted cyclopentanols to have shorter retention times than the trans alcohols. These methods permitted the ready identification of the products and the relative ratio of the diastereoisomers.

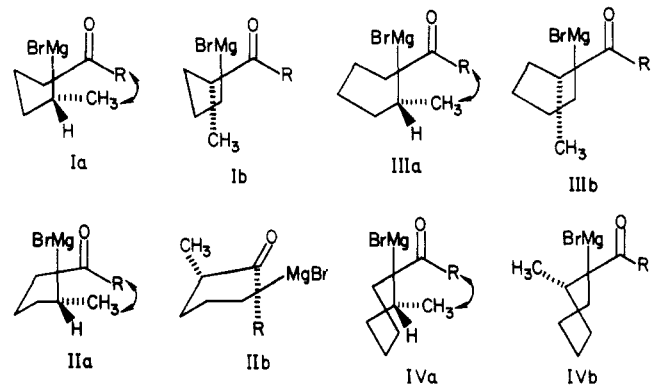
The diastereoselectivity of these reactions must reside in the cyclization step, the second nucleophilic attack of the 5-oxoalkyl Grignard reagent (Scheme II). Since the primary or the secondary Grignard may be responsible for the first reaction with the ester carbonyl, two intermediates, a and b, are possible.

Significantly lower yields of the cyclized products were obtained when 1,5-bis(bromomagnesio)hexane (**2**) was reacted with some of the same esters (**3**, **4**, and **8**). Analysis of the products showed that in the six-membered cyclization, in contrast to the five-membered, competitive inter- and intramolecular processes became relatively important. While the 2-methyl-1-substituted cyclohexanols were isolated in only 53% to 57% yield, the trans diastereoisomers were still greatly favored over the cis (Table III).

At the moment of cyclization, several conformations leading to 2-methyl-1-substituted-cyclopentanols are possible (Ia, Ib, IIa and IIb, Scheme III). In both Ia and IIa there are important steric interactions between the methyl group originating in the reagent and the R group from the original ester. The expected greater reactivity of the secondary center of the di-Grignard reagent suggests that the favored intermediates should be Ib and IIb. The same argument leads to the intermediacy of conformations IIIb and IVb to explain the diastereoselection in the six-membered annelations.

Currently we are undertaking experiments to determine conclusively whether it is the secondary or primary part

Scheme III



of the di-Grignard which initiates the first attack on the ester carbonyl since this information is critical to all discussion concerning the origin of the selectivity.

Registry No. **1**, 63452-95-9; **2**, 101934-18-3; **3**, 109-94-4; **4**, 141-78-6; **5**, 105-37-3; **6**, 5452-75-5; **7**, 3289-28-9; **8**, 93-89-0; **9**, 94-08-6; **10**, 7335-27-5; **11**, 94-30-4; *cis*-**12**, 25144-05-2; *trans*-**12**, 25144-04-1; *cis*-**13**, 16467-04-2; *trans*-**13**, 16467-13-3; *cis*-**14**, 16467-06-4; *trans*-**14**, 16467-12-2; *cis*-**15**, 101934-19-4; *trans*-**15**, 101934-20-7; *cis*-**16**, 22865-13-0; *trans*-**16**, 22862-81-3; *cis*-**17**, 22865-14-1; *trans*-**17**, 22865-01-6; *cis*-**18**, 75968-43-3; *trans*-**18**, 101934-21-8; *cis*-**19**, 75968-45-5; *trans*-**19**, 101934-22-9; *cis*-**20**, 75968-44-4; *trans*-**20**, 101934-23-0; *cis*-**21**, 7443-70-1; *trans*-**21**, 7443-52-9; *cis*-**22**, 19879-11-9; *trans*-**22**, 19879-12-0; *cis*-**23**, 30689-79-3; *trans*-**23**, 30689-80-6; $Br(CH_2)_3CH(CH_3)Br$, 626-87-9; $Br(CH_2)_4CH(CH_3)Br$, 627-96-3.

P. Canonne,* M. Bernatchez
Département de chimie
Faculté des sciences et de génie
Université Laval
Québec (Québec), Canada G1K 7P4
Received September 13, 1985

(9) (a) Rei, M.-H. *J. Org. Chem.* **1978**, *43*, 2173. (b) Battioni, J. P.; Capmau, M. L.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1969**, 976. (c) Battioni, J. P.; Chodkiewick, W. *Bull. Soc. Chim. Fr.* **1969**, 981. (d) Lemière, G. L.; Dommisse, R. A.; Alderweireldt, F. C. *Bull. Soc. Chim. Belg.* **1977** *86*, 737. (e) Eliel, E. L.; Shroeter, S. H.; Brett, T. J.; Biros, F. J.; Richer, J. C. *J. Am. Chem. Soc.* **1966**, *88*, 3327. (f) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1978**, *100*, 545.

(10) (a) Rei, M.-H. *J. Org. Chem.* **1979**, *44*, 2760. (b) Grenier-Loustalot, M. F.; Zahidi, A.; Bonastre, J.; grenier, P. *Bull. Soc. Chim. Fr.* **1979**, 229. (c) Senda, Y.; Ishiyama, J.; Imaizumi, S. *Tetrahedron*, **1975**, *31*, 1601. (d) Rutherford, K. G.; Wassenaar, S.; Brien, J. F.; Fung, D. P. C. *Can. J. Chem.* **1971**, *49*, 4116. (e) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1978**, *100*, 545.

Stereoselective Total Synthesis of (±)-Isocelorbicol

Summary: The naturally occurring trihydroxyagarofuran (±)-isocelorbicol (**1**) has been synthesized in 15 steps (3.2%) from 9-keto-α-agarofuran (**2**). This completely stereoselective synthesis includes an osmium tetraoxide oxidation in which the reagent attacks exclusively from the more hindered face of the molecule.

Sir: Isocelorbicol (**1**)[1] is one of a number of complex, polyhydroxylated derivatives of agarofuran which are found in many plants of the family Celastraceae.[2] Although no member of this group of natural products has been shown to possess biological activity, several ester alkaloids based on these sesquiterpenoids have been isolated from *Catha edulis* (khat) a stimulant narcotic used in the Middle East and parts of Africa.[3] Isocelorbicol, although one of the more structurally simple members of this group of natural products still presents a considerable

(1) Smith, C. R.; Miller, R. W.; Weisleder, D.; Rohweder, W. K.; Eikman, N.; Clardy, J. *J. Org. Chem.* **1976**, *41*, 3264.

(2) Smith, R. A. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1977; Vol. 16, pp 215–248. Smith reviews this class of sesquiterpenes and the derived ester alkaloids.

(3) (a) Baxter, R. C.; Crombie, L.; Simmonds, D. J.; Whiting, D. A.; Braenden, O. J.; Szendrei, K. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2965. (b) Crombie, L.; Crombie, W. M. L.; Whiting, D. A.; Szendrei, K. *Ibid.* **1979**, 2976. (c) Baxter, R. C.; Crombie, W. M. L.; Crombie, L.; Simmonds, D. J.; Whiting, D. A.; Szendrei, K. *Ibid.* **1979**, 2982.

0022-3263/86/1951-2148$01.50/0