Table I. Characteristics of Liquid–Liquid Chromatographic Runs with (*RR*)-**1** as Host Compound in Mobile Phase

Run no.	Comp resolved No.	mg	*T*, °C	Separation factor (α)	EDC[a] (D_A/D_B)	Theoretical plates (N)	Resolution R_s	Area A/ Area B[b]	—([H]/[G])$_{max}$[c]— A	B
1[d]	**2**	200	0	1.76	1.78	24	0.6	0.94	4.5	8
2[e]	**2**	25	25	1.52	1.48	19	0.6		65	136
3[f]	**3**	100	−13	2.48	2.48	18	1.25	1.08	2.1	3.3
4[g]	**4**	108	−15	3.6	5	18	1.57	0.83	8.6	25
5[h]	**4**	100	−15	2.4		74	1.28		2.7	4.1

[a] Reference 2. [b] Ratios of integrated areas under peaks with A the faster and B the slower moving enantiomer. [c] Ratios of concentrations of host to guest at the tops of peaks of plots. [d] Column, 57 by 2.5 (i.d.) cm, packed with (by weight) 66% Celite and 5% $NaPF_6$ (0.94 *M*) in 29% H_2O, gravity flow (0.30 ml/min), host 0.0375 *M* in $CHCl_3$. [e] Column, 60 by 0.76 (i.d.) cm, packed with (by weight) 34% silica gel and 9% $NaPF_6$ (0.94 *M*) in 57% H_2O, pressure drop 30 psi (0.15 ml/min), host 0.0375 *M* in $CHCl_3$. [f] Column, 60 by 0.76 (i.d.) cm, packed with (by weight) 40% silica gel and 19% $NaPF_6$ (2.4 *M*) in 41% H_2O, pressure drop 80 psi (0.50 ml/min), host 0.0375 *M* in $CHCl_3$. [g] Column, 60 by 0.76 (i.d.) cm, packed with (by weight) 41% silica gel and 26% $LiPF_6$ (4.0 *M*, pH 4) in 33% H_2O, pressure drop 22 psi (0.52 ml/min), host 0.0750 *M* in $CHCl_3$. [h] Column identical with run 4 except dichloromethane was substituted for chloroform.

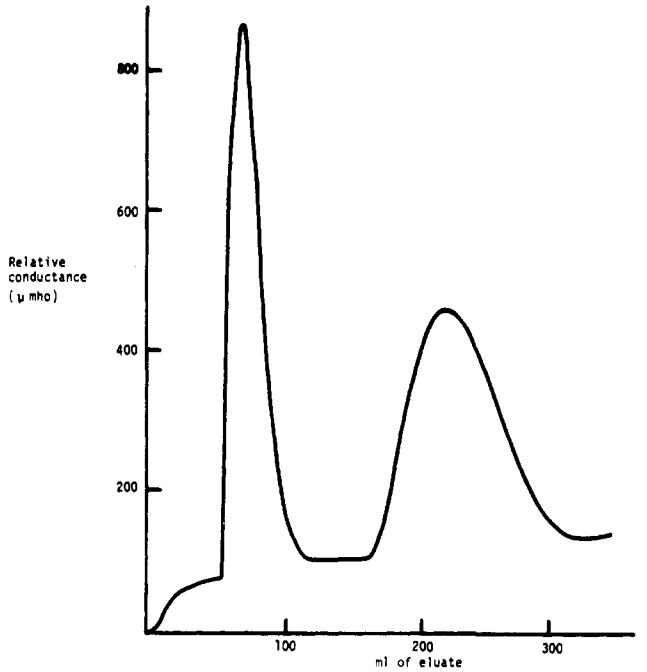
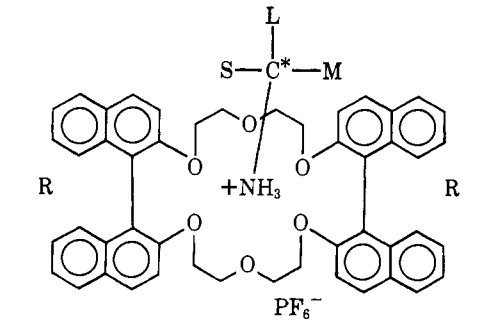


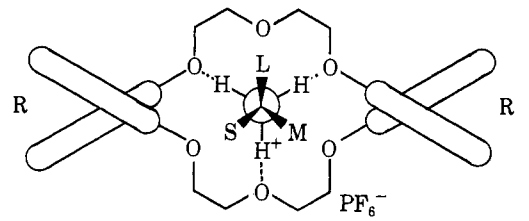
Figure 3. Chromatographic optical resolution by (*RR*)-**1** of methyl *p*-hydroxyphenylglycinate hexafluorophosphate salt.

EDC, as is nearly observed in the four runs (Table I).[4] Thus knowledge of EDC values for a variety of amino esters indicates the viability of their resolution by this technique. The values of (area A)/(area B) which ideally should be unity varied from 0.83 to 1.08, probably due to nonlinearity of the conductance. The values of ([H]/[G])$_{max}$ (Table I) provide a measure of the complexing efficiency by the host of the guest. As expected, they are greater for the B component. At full complexing utility of the host, these values should approach unity. They ranged from 2.1 to 136. By choice of solvent and host concentration for the mobile phase (compare runs 4 and 5), and inorganic salt concentration in the stationary phase, the column parameters can be manipulated to best accommodate the hydrophilicity–lipophilicity and binding capacities of the guest compounds.

These results demonstrate that by rational design of host compounds, complete optical resolution by highly



Complexes of (*RR*)-1 with generalized salts



More stable complexes of (*RR*)-**1**
(*S*)-**2**, L = C_6H_5, M = CH_3, S = H
(*R*)-**3**, L = C_6H_5, M = CO_2CH_3, S = H
(*R*)-**4**, L = *p*-HOC_6H_4, M = CO_2CH_3, S = H

structured complexation of guest compounds can be accomplished.

(6) National Institutes of Health Postdoctoral Fellow.

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Halopolycarbon Homologation

Sir:

The functional homologation of organic structures is usually limited to two or three carbon segments by virtue of the availability and cost of reagents.[1] Recently several examples of functionalized multicarbon homologation have been reported.[2] However, the construc-

(1) Two-carbon homologation: (a) RX + malonic or acetoacetic ester; (b) RX + acetylene; (c) RMgX + ethylene oxide. Three-carbon homologation: (a) RX + $^-C{\equiv}CCH_2O^-$; (b) RMgX + $ClCH_2CH{=}CH_2$.

(2) A. Suzuki, N. Miyaura, M. Itoh, H. C. Brown, G. W. Holland, and E. Negishi, *J. Amer. Chem. Soc.*, **93**, 2792 (1971); E. Negishi and H. C. Brown, *Synthesis*, 196 (1972).

tion of branched chain functional derivatives is cumbersome and is usually accompanied with low attendant yields.

One approach is to use protected alkyl halides or mono-Grignard reagents of dihalides, such as **1** or **2**.

$$\underset{\textbf{1, R = THP-, Me}_3\text{Si, EtO(CH}_3\text{)CH-}}{\text{RO(CH}_2)_n\text{MgX}} \qquad \underset{\textbf{2}}{\text{Y(CH}_2)_n\text{MgX}}$$

Examples of the use of **1** have been reported and serve as useful routes to the preparation of alcohols and products derivable therefrom.[3] Unfortunately it is not possible to synthesize mono-Grignard reagents of the type **2** when X = Y = Br or Cl.[4] Only when X and Y are different is this possible.[5] However, such compounds with the exception of $ClCH_2CH_2CH_2Br$ (which incidentally affords cyclopropane with magnesium)[6] are not readily available.

We wish to report at this time a general convenient route for the halopolycarbon homologation of various alkyl and aryl Grignard reagents by the dilithium tetrachlorocuprate catalyzed[7] coupling with α,ω-dibromoalkanes. This is a simple approach to the preparation in moderate to excellent yield, of a wide variety of (branched) aliphatic, alicyclic, and aromatic compounds (**3**) that heretofore have been relatively inaccessible. These are valuable functionalized products that can be directly utilized in further synthetic elaboration.

$$\text{RMgX} + \text{Br(CH}_2)_n\text{Br} \xrightarrow[\text{THF}]{\text{Li}_2\text{CuCl}_4} \underset{\textbf{3}}{\text{R(CH}_2)_n\text{Br}} + \text{R(CH}_2)_n\text{R}$$

$$n = 3, 4, 5, 6, 10$$

The halopolycarbon homologation is effected by adding a THF solution of the Grignard reagent to a well-cooled stirred solution of an equimolar quantity of the α,ω-dibromide in the presence of a catalytic amount of lithium tetrachlorocuprate.[8] Yields can be increased somewhat by using an excess of the dibromide, but it is usually not worth the effort.

To help establish the scope of the reaction, simple readily available precursors such as isopropyl, *sec*- and *tert*-butyl, *tert*-amyl, cyclohexyl, and phenyl Grignard reagents were coupled with various α,ω-dibromoalkanes to give the corresponding branched (or substituted) 1-bromoalkanes (**3**) (Table I).

Table I. Dilithium Tetrachlorocuprate Catalyzed Alkylation of α,ω-dihalides with Grignard Reagents[a]

Grignard reagent	$Br(CH_2)_nBr$, n	% yield (isolated), $R(CH_2)_nBr$: Based on RX	% yield (isolated), $R(CH_2)_nBr$: Based on $Br(CH_2)_nBr$
i-PrMgCl	3	68	85
i-PrMgCl	4	49	68
i-PrMgBr	5	56	80
i-PrMgCl	5	55	70
i-PrMgCl[b]	5	35	60
i-PrMgCl[c]	5	45	73
i-PrMgCl	6	52	64
i-PrMgCl	10	47	56
sec-BuMgBr	4	60	69
sec-BuMgBr	5	50	54
t-BuMgCl	5	53	76
IsoamylMgBr	3[d]	80	80[e]
CyclohexylMgCl	5	54	96
C_6H_5MgBr	5	46	77

[a] Reaction conditions: Grignard reagent in THF (~2 *M*) was slowly added to a stirred cooled (5–10°) solution of an equivalent of $Br(CH_2)_nBr$ in THF (2–2.5 *M*) containing ~10 mequiv of Li_2CuCl_4. Mixture was stirred for an additional 1 hr and worked up. Product was isolated by a rough fractional distillation through a short column at reduced pressure and characterized and identified by nmr, ir, and comparison of boiling point and refractive index with literature values. The only contaminant in varying amounts was unreacted α,ω-dibromide. This could be removed by better fractionation. [b] In THF–benzene solution with a 1.2:1 ratio of THF to Grignard reagent. [c] In THF–benzene solution with a 2:1 ratio of THF to Grignard reagent, 1.2 mol equiv of THF was added during the preparation of the Grignard reagent, while 0.8 mol equiv of THF was added, in the second step, to the dibromide benzene solution. [d] $Br(CH_2)_3Cl$ was used. [e] Product isolated was $R(CH_2)_nCl$.

Selected examples of the synthetic advantage of this technique follow. Isooctyl bromide, an important intermediate in the Wittig synthesis of disparlure (*cis*-7,8-epoxy-2-methyloctadecane) the sex attractant of the gypsy moth, is easily prepared by the reaction of either isopropyl, isobutyl, or isoamyl magnesium chlorides or bromides with the respective α,ω-dibromoalkane.[9] The choice of reactant partners is dictated primarily by economics and availability. Heretofore isooctyl bromide was available in low to moderate yield *via* a multistep synthetic sequence.

6-Methyl-1-bromooctane (anteisononyl bromide) is a component in the synthesis of 14-methyl-(*Z*)- and (*E*)-8-hexadecenols, sex hormones emitted by various stored grain beetles (*Trogoderma inclusum, granarium* and *glabrum*), and is prepared in one step in ~70% yield from *sec*-butyl magnesium bromide and 1,5-dibromopentane. On the other hand optically active material is easily available from 2-methylbutyl magnesium bromide and 1,4-dibromobutane.[10]

(3) (a) J. L. Speier, U. S. Patent 2,640,067 (1953) (assigned to Dow-Corning); *Chem. Abstr.*, **48**, 5206*i* (1954); (b) R. Achard and J. Morel, French Patent 1,322,911 (1963) (assigned to Rhone-Poulenc S.A.); *Chem. Abstr.*, **59**, 11262*d* (1963); (c) P. Mazerolles, *Bull. Soc. Chim. Fr.*, 464 (1965); (d) P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37**, 1947 (1972); (e) coupling of Grignard reagents with 2-chloroethanol and 3-chloropropanol gives the corresponding alcohols in variable yields which seem to be dependent upon the nature of the Grignard reagent, J. B. Conant and W. R. Kirner, *J. Amer. Chem. Soc.*, **46**, 240 (1924), and references contained therein.

(4) P. Chuit, *Helv. Chim. Acta*, **9**, 264 (1926); C. D. Nenitzescu and I. Necsoiu, *J. Amer. Chem. Soc.*, **72**, 3483 (1950); R. Lukes and V. Dudek, *Collect. Czech. Chem. Commun.*, **24**, 2484 (1959); H. Normant and M. Nöel, *C. R. Acad. Sci.*, **253**, 2237 (1961).

(5) M. Nöel, J. C. Combret, Y. Leroux, and H. Normant, *C. R. Acad. Sci., Ser. C*, **268**, 1152 (1969).

(6) N. Domanitzkii, *J. Russ. Phys. Chem. Soc.*, **47**, 1790 (1915), *Chem. Abstr.*, **10**, 3062 (1916); C. F. H. Allen, C. V. Wilson, and W. L. Ball, *Can. J. Res.*, **9**, 432 (1933).

(7) (a) M. Tamura and J. K. Kochi, *Synthesis*, 303 (1971). See also G. Foquet and M. Schlosser, *Angew. Chem., Int. Ed. Engl.*, **13**, 82 (1974). (b) The only examples of monosubstitution of α,ω-dihaloalkanes with organometallic reagents are that of various alkynyl lithiums and α,ω-diiodoalkanes: G. Grimmer and J. Kracht, *Chem. Ber.*, **96**, 3370 (1963); S. Nimgirawath, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **26**, 183 (1973).

(8) Coupling can also be effected in benzene–THF mixtures but not in dibutyl ether.

(9) *Cf.* H. S. Bestmann and O. Vostrowsky, *Tetrahedron Lett.*, 207 (1974). Alternatively, isooctyl chloride can be synthesized in ~80–85% yield from isoamyl magnesium chloride or bromide and commercially available 1-chloro-3-bromopropane. Isoheptylbromide can be similarly prepared for its use in an acetylene based synthesis of disparlure. *Cf.* K. Eiter, *Angew. Chem., Int. Ed. Engl.*, **11**, 60 (1972).

(10) *Cf.* J. I. DeGraw and J. O. Rodin, *J. Org. Chem.*, **36**, 2902 (1971).

3-Anteisotridecenoic acid and 3-isododecenoic acid are part of the fatty acid components of the peptide antibiotic amphomycin[11] and these are now easily synthesized by halopolycarbon homologating *sec*-butyl (or 2-methylbutyl) and isobutyl Grignard reagents, respectively.

With the ready availability of 1-chloro-3-bromopropane[12] and the homologous even-numbered alkyl alcohols and halides, the synthesis of the less accessible odd-numbered alkyl chlorides such as tridecyl and pentadecyl chlorides[13] is easily accomplished in excellent (80–90%) yield.

The application of the halopolycarbon homologation technique to the synthesis of long chain α,ω-dibromides is exemplified by the synthesis of 1,18-dibromooctadecane in 70–80% yield from 1,6-hexanedimagnesium chloride and 1,6-dibromohexane.

Halo dicarbon homologation does not occur[14] with ethylene chlorobromide or dibromide. Instead ethylene[15] (evolved as a gas and identified) and the alkyl halides (RX) are formed. The alkyl halides undergo further (coupling) reaction with the starting Grignard reagent to afford R–R′.

$$RMgX + Br(CH_2)_2Y \longrightarrow RBr(Y) + MgXBr(Y) + CH_2{=}CH_2 \quad (1)$$

$$RMgX + RBr(Y) \xrightarrow{Li_2CuCl_4} R\text{–}R + MgXBr(Y) \quad (2)$$
$$X, Y = Cl, Br$$

Since approximately 50–60% of the dihaloethane was covered, it is apparent that reaction **2** is faster than **1**.

Preliminary work indicates that the reaction of alkyl and aryl lithium reagents with α,ω-dibromoalkanes in the absence of Cu (I or II) but in the presence of TMEDA may be a useful alternative. In the absence of TMEDA extensive halogen–metal exchange occurs and the reaction has no synthetic value.[16]

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(17) On leave of absence from the Ben-Gurion University of the Negev, Be'er-Sheva, Israel.

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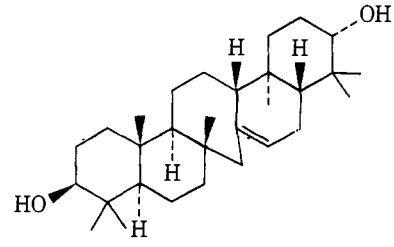
Application of Nonenzymic Biogenetic-Like Olefinic Cyclizations[1] to the Total Synthesis of *dl*-Serratenediol

Sir:

Serratenediol (**1**),[2] a member of a recently discovered class of pentacyclic triterpenoids having a seven-membered C ring.[2,3] contains nine asymmetric centers; hence a feasible total synthesis requires a plan involving a very high degree of stereoselectivity. We envisaged such a scheme based on the biogenetic-like cyclization of a tetraenic alcohol such as **2**, which seemingly had



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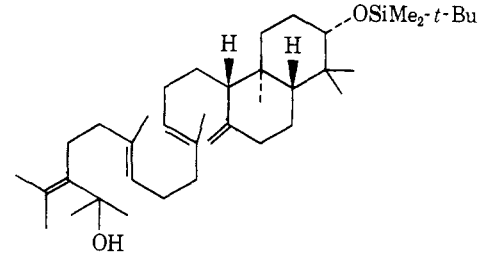

2

promise of leading to a substance, **15**, having the complete serratene ring system. The present communication contains an account of the successful reduction of this plan to practice.

The cyclization substrate **2** was produced as follows. The known tricyclic ketone **8**[4] was prepared by a new method (see Scheme I) based on the olefinic cyclization **6** → **7**. The allylic alcohol **3**,[5] obtained by reaction

(1) For a recent paper in this series see W. S. Johnson, K. Wiedhaup, S. F. Brady, and G. L. Olson, *J. Amer. Chem. Soc.*, **96**, 3979 (1974).

(2) (a) T. Ysuda, T. Sano, K. Kawaguchi, and Y. Inubushi, *Tetrahedron Lett.*, 1279 (1964); (b) Y. Inubushi, Y. Tsuda, T. Sano, T. Knoita, S. Suzuki, H. Ageta, and Y. Otake, *Chem. Pharm. Bull.*, **15**, 1153 (1967).

(3) J. W. Rowe, *Tetrahedron Lett.*, 2347 (1964).

(4) G. Stork, A. Meisels, and J. E. Davis, *J. Amer. Chem. Soc.*, **85**, 3419 (1963).

(5) The formulas depict only one enantiomer of a racemic pair. The nmr and ir spectra of all specimens were consistent with the assigned structures. Moreover, new compounds which could be distilled or crystallized gave satisfactory combustion analyses. Yields are reported for distilled, chromatographed, or recrystallized substances only.

(11) (a) M. Bodanszky, G. F. Sigler, and A. Bodanszky, *J. Amer. Chem. Soc.*, **95**, 2352 (1973); M. Bodanszky, N. C. Chaturvedi, and J. A. Scozzie, *J. Antibiot.*, **22**, 399 (1969). (b) For more cumbersome alternative routes to the synthesis of iso and anteiso series of alcohols and acids see A. H. Milburn and E. V. Truter, *J. Chem. Soc.*, 3344 (1954).

(12) (a) Dow Chemical Corporation, Michigan Chemical Corporation. Related reactions are the following. (b) Recently it was shown that vinyl copper(I) reagents prepared by addition of alkyl copper(I) to 1-alkynes selectively displaces iodide from 1-chloro-3-iodopropane. J. F. Normant, G. Cahiez, C. Chuitt, and J. Villieras, *Tetrahedron Lett.*, 2407 (1973). (c) Chloroiodoethylene reacts selectively with alkynyl- and perfluoralkylcopper(I) to give the corresponding chlorovinyl derivatives. J. Burdon, P. L. Coe, C. R. Marsh, and J. C. Tatlow, *J. Chem. Soc., Perkin Trans. 1*, 639 (1972).

(13) These compounds (*i.e.*, the corresponding bromides) are usually prepared from the commercially available fatty acids (C_{12}–C_{18}) *via* the Hunsdiecker reaction or the Cristol–Firth modification: S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961). *Cf.* A. Roedig in "Methoden der Organischen Chemie," Vol. 5, part 4, E. Müller, Ed., George Thieme Verlag, Stuttgart, 1960, p 488; C. V. Wilson, *Org. React.*, **9**, 332 (1957).

(14) On the other hand, 2-bromoethyl tosylate reacts selectively with lithium dibutyl cuprate at −78° to give hexyl bromide. At higher temperatures (−20°) dialkylation occurs, *i.e.*, decane is the only product. C. R. Johnson and G. A. Dutra, *J. Amer. Chem. Soc.*, **95**, 7777 (1973). Uncomplexed organolithium cleaves alkyl tosylates *via* S–O scission. L. Friedman and R. J. Honour, unpublished results.

(15) The formation of olefins from the reaction of organometallic reagents (reductive elimination or dehalogenation) with vicinal dihalides is well established. M. Mousseron and F. Winternitz, *Bull. Soc. Chim. Fr.*, **13**, 604 (1946); L. Skattebol, *Tetrahedron*, **21**, 1357 (1965); G. H. Posner and J. S. Ting, *Syn Commun.*, **3**, 281 (1973).

(16) For the parameters affecting the reaction of organolithium reagents and alkyl halides see R. J. Honour, Ph.D. Thesis, Case Western Reserve University, 1970.