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Beyond Erythro and Threo. A Proposal for Specifying Relative Configuration in Molecules with Multiple Chiral Centers

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Since erythro and threo are ambiguous descriptors of relative configuration, a new system is proposed that utilizes the descriptors pref (priority reflective) and parf (priority antireflective). The relationship between two contiguous chiral centers is pref if the order of decreasing sequence-rule priority of the three remaining groups at one center is a reflection of the order of decreasing sequence-rule priority of the groups at the other. When the orders of decreasing sequence-rule priorities at the two centers are not reflections of each other, the relative configuration is parf. Examples of the nomenclature system are given. Extensions of the system to molecules with noncontiguous chiral centers and to molecules with more than two chiral centers are described. An informal nomenclature using the descriptors SYNCAT and ANCAT is suggested for use in communicating the sense of relative steroechemistry in acyclic and macrocyclic molecules. It is based on comparing substituents according to their steric bulk, and when like substituents are disposed to the same side of a molecule in its extended zig-zag conformation, the relative configuration is said to be SYNCAT (syn-catenoid). When like substituents are on opposite sides of the chain, the relative configuration is ANCAT (anti-catenoid).

Introduction

The stereochemical descriptors erythro and threo suffer from the same limitations as do D and L and cis and trans. Each set depends on an ability to identify analogous or related substituents. As is well known, ambiguities can arise with all of these descriptors, and subjective judgments unfortunately attend their use. The sequence rule of the Cahn–Ingold–Prelog convention has been applied to each stereochemical situation treated by the older descriptors and has removed all elements of ambiguity by utilizing a system of substituent priority based on atomic number and a carefully considered group of subrules.[2] The Cahn–Ingold–Prelog system is the basis of the most recent IUPAC rules on stereochemistry. These rules, which use the descriptors *R* and *S* for chiral centers and *Z* and *E* for double-bond stereochemistry, have received broad acceptance.[3] When a molecule contains two chiral centers, each has its configuration assigned independently as *R* or *S*. If one is dealing with a stereoisomer of known relative but unknown absolute configuration, the IUPAC rules specify that the enantiomer having the *R* configuration at the lowest-numbered chiral center be arbitrarily assumed, and the configurational descriptors that result be identified by a superscript asterisk, e.g., *R**, *S** (pronounced *R*-star, *S*-star). For the frequently encountered case of a racemate, the designations (*RS*) vs. (*SR*) are specified. This portion of the system is not generally used by most organic chemists, is somewhat cumbersome, and has not displaced the erythro, threo terminology (see footnote 13).

Erythro and threo as stereochemical descriptors in carbohydrate nomenclature are well established and clearly defined.[4] Extension to structures containing a richer variety of substituents and functional groups has, however, bred confusion. In one extension, substituents are ranked as small, medium, or large according to their steric requirements with like substituents aligned on the same side of the main chain in a Fischer projection of the erythro configuration.[5] Since, however, it is not always clear which substituent is larger than another, this approach can be ambiguous.

The point has been reached where it is now customary for authors to specify exactly what their descriptors mean

(1) (a) University of Virginia. (b) University of Vermont.

(2) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385–415.

(3) (a) "IUPAC Nomenclature of Organic Chemistry", Pergamon Press, Oxford, 1979, Section E. (b) *J. Org. Chem.* **1970**, *35*, 2849–2867. (c) *Pure and Appl. Chem.* **1976**, *45*, 11–30.

(4) IUPAC Commission on the Nomenclature of Organic Chemistry (CNOC) and IUPAC–IUB Commission on Biochemical Nomenclature (CBN), *Biochemistry*, **1971**, *10*, 3983–4004.

(5) Barton, D. H. R.; Cookson, R. C. *Q. Rev., Chem. Soc.* **1956**, *10*, 44–82. In this account, which sets out the principles of conformational analysis, a correlation between relative configuration and thermodynamic stability is noted. In the most simple cases, because the preferred staggered form of the erythro diastereomer allows for minimum van der Waals repulsions between substituent groups, it is more stable than the threo diastereomer.

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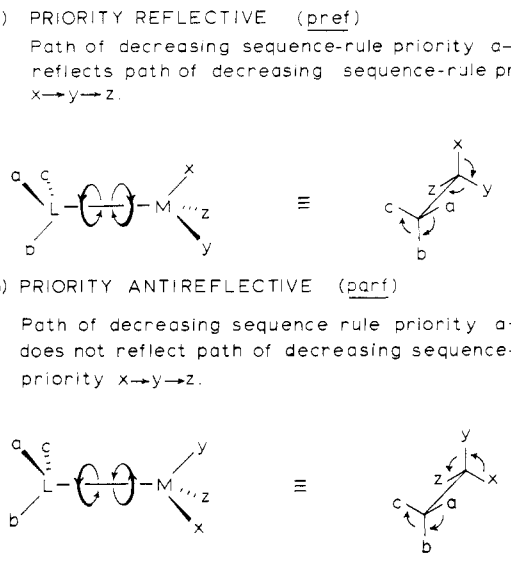
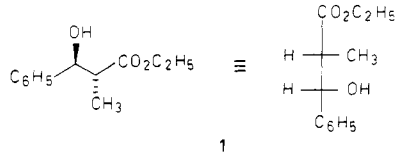


Figure 1. Relative configuration of two adjacent chiral centers according to whether they are sequence-rule priority reflective (pref) or are not sequence-rule priority reflective (parf).

in each particular paper. In a recent article, it was noted that the relative configuration of hydroxy ester 1 was threo



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according to the system used there, while another interpretation of how carbohydrate-based terminology might be extended to acyclic stereochemistry would assign to 1 the erythro configuration because the methyl and hydroxy groups both project to the right in a Fischer projection formula,[6] a conclusion also reached with the group-size convention.[5]

The next paper in the same issue of this journal stated, "The terms erythro and threo ... conform to usage by most of the groups working on aldol-type additions. It should be made clear that this usage is contrary to the rules defined by Chemical Abstracts or Beilstein."[7]

The need for a systematic approach toward specifying relative configuration is clear. Some recent suggestions have been advanced in which assignment of erythro and threo descriptors is tied to sequence-rule priority.[8-10] This general notion is a reasonable one with much to commend it as the direction to take. Schemes that regularize the use of erythro and threo, however, are burdened with the past inconsistent application of these two terms. What is needed is a new set of descriptors, derivable from sequence-rule considerations, for specifying the relative configuration in molecules with multiple chiral centers.

This paper presents a system for accomplishing these ends. The system that is proposed is an easy to use application of the sequence rule. It employs two new descriptors of relative configuration, priority reflective (pref) and priority antireflective (parf), and can be applied to either acyclic or cyclic structures containing any number

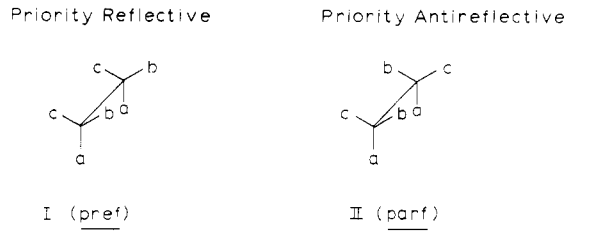


Figure 2. When two chiral centers are equivalently substituted, relative configuration pref corresponds to meso.

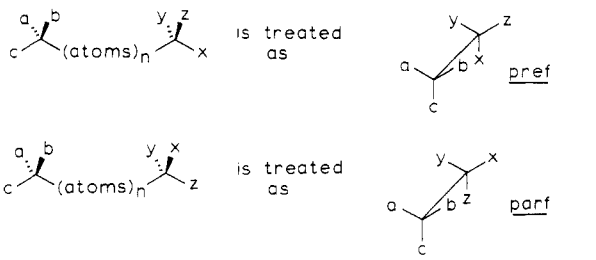


Figure 3. Procedure for specifying relative configuration when the chiral centers are not contiguous neglects intervening atoms and considers chiral centers as if they were directly linked.

of contiguous or noncontiguous chiral centers.[11]

Definitions and Applications of the Descriptors Pref and Parf

General cases that define the two descriptors pref and parf are shown in Figure 1. Two bonded atoms of tetrahedral coordination L and M bear substituents a, b, c and x, y, z, respectively. The orders of decreasing sequence-rule priority at the two centers are a > b > c and x > y > z. When (Figure 1a) the substituents at one center (L) trace a path from highest priority to lowest priority (a → b → c), which is the reflection of the path from highest priority to lowest priority (x → y → z) at the other (M), the relative configuration at the two chiral centers is priority reflective (pref). When reflection symmetry between the decreasing sequence-rule circuits at the two carbons is absent (Figure 1b), the relative configuration is priority rule antireflective (parf).

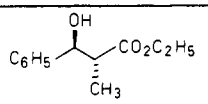
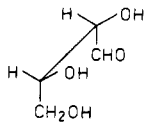
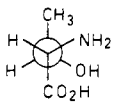
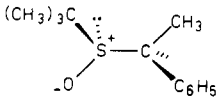
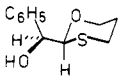
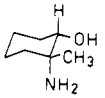
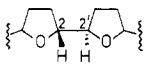
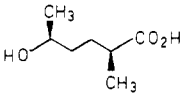
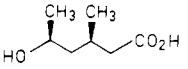
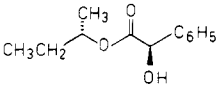
Notice that it is the paths of decreasing sequence-rule priority that are compared, not the absolute positions of the substituents themselves. Therefore, this method of specifying relative configuration is independent of conformation. However, it should also be noted that with equal substituents at the two tetrahedral atoms L = M, i.e., a = x, b = y, c = z, the meso diastereomer, which is priority reflective (pref), can be displayed in the customary eclipsed conformation I, showing this internal reflection, while the chiral diastereomer II is portrayed as nonreflective or antireflective (parf).[12] This relationship is shown in Figure 2.

Relative configuration pref is that which obtains when the re face of one atom is bonded to the si face of another.

(6) Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296–1309.
(7) Hoffman, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309–1314.
(8) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1980**, *45*, 3549–3554.
(9) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106–2108.
(10) IUPAC Commission on Macromolecualr Nomenclature Recommendations 1980, *Pure and Appl. Chem.* **1981**, *53*, 733–752.

(11) The two authors independently arrived at similar approaches to the problem of specifying relative configuration, and the present article is joint revision of previously submitted individual manuscripts. During the preparation of this manuscript, we became aware of yet another related approach: Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.*, in press. We thank Professors Seebach and Prelog for advising us of their interest in this problem and for a preprint of their manuscript.
(12) The reflective–antireflective concept for two relative configurations I and II is pictorially descriptive and thus does not require memorization of new terms with danger of reversed recall. The terminology and acronyms can be used in the common western languages without translation. The term antireflective rather than nonreflective was chosen to facilitate formation of an acronym and to avoid the need for translation.

Chart I. Relative Configuration According to the Pref-Parf System of Nomenclature

entry[a]	compound[b]	decreasing priority order of substituents	descriptor[c]
1		C(2): $CO_2C_2H_5$, CH_3, H C(3): OH, C_6H_5, H	parf
2[d]		C(2): OH, CHO, H C(3): OH, CH_2OH, H	pref
3[e]		C(2): NH_2, CO_2H, H C(3): OH, CH_3, H	parf
4		S: O, $(CH_3)_3C$, lone pair C: C_6H_5, CH_3, H	pref
5[f]		exocyclic C: OH, C_6H_5, H ring C: S, O, H	pref
6		C(1): NH_2, CH_2C, CH_3 C(2): OH, CH_2, H	pref
7[g]		C(2): O, CH_2, H C(2′): O, CH_2, H	parf
8		C(2): CO_2H, CH_3, H C(5): OH, CH_3, H	parf
9		C(3): CH_2CO_2H, CH_3, H C(5): OH, CH_3, H	pref
10		*sec*-butyl: CH_3CH_2, CH_3, H mandelate: OH, C_6H_5, H	parf

[a] For simplicity, entry number and compound number are the same and are numbered sequentially throughout the paper. [b] Only a single enantiomer is shown in each case. The pref-parf descriptor is, of course, the same for the mirror image of each compound. [c] The descriptor is incorporated into the systematic name of the compound as a prefix. For example, compound 1 is ethyl *parf*-3-hydroxy-2-methyl-3-phenylpropanoate. [d] D-Erythrose. [e] L-Threonine. [f] A simplified example of a structural type described by Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem Soc.* **1978**, *100*, 1614-1616. [g] Schultz, W. J.; Etter, M. C.; Pocius, A. V.; Smith, S. *J. Am. Chem. Soc.* **1980**, *102*, 7981-7982.

Relative configuration parf is that which obtains when two faces of like prochirality (re–re or si–si) are connected.[13]

Chart I gives examples of the application of this system. The first three entries illustrate straightforward application to molecules with adjacent chiral carbon atoms. As demonstrated by entry 4 in the chart, the system is also nicely suited to the specification of relative configuration involving chiral centers other than carbon.

Entries 5 and 6 depict relative configuration in substances that have one (5) or both (6) chiral atoms in a ring. In entry 7, the two chiral centers connect two different tetrahydrofuran units of a synthetic polyether.

Two Nonadjacent Chiral Centers

In a structure with two nonadjacent chiral centers, one simply neglects the intervening bonds and treats the two centers as if they were directly linked as shown in Figure 3.

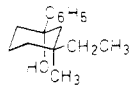
Entries 8–10 in Chart I illustrate the application of the pref–parf descriptors to molecules with two noncontiguous chiral centers.

For cases where one or both of two noncontiguous chiral centers are part of a ring, we imagine them to be connected by a bond that replaces the shorter path. Thus, 11 is treated as if it were 11′ and the relative configuration between the two chiral centers is parf. Compound 12 is treated as if it were 12′ and is pref.

When two chiral centers are connected by nonidentical molecular fragments of equal length, the lower priority fragment is replaced by an imaginary connection and the

(13) While the use of *R** and *S** or (*RS*) and (*SR*) will give a stereochemical structural definition for a molecule, this definition does not describe a *relative stereochemical relationship* at two chiral centers, independent of their connection. Since *R**, *S**, or (*RS*) and (*SR*) configurations are defined by four substituents at each center, the relative configurations at any two directly or indirectly connected centers will depend on the Cahn–Ingold–Prelog priority of this connection. Thus, for two distant centers, *R**, *S**, or (*RS*) and (*SR*) assignments of either or both may change with changes on the connecting portion of the molecule, even though the bonds at the two centers are held constant. In the *pref–parf* definition of relative stereochemistry, where assignment of relative stereochemistry is independent of the connection of the two centers, an assignment of relative stereochemistry is governed only by three substituents at each center. Thus, a pref or parf assignment will remain constant with substitutions, oxidations, reductions, or other changes on a linking protion of the molecule, while *R**, (*RS*), or *S**, (*SR*) assignments may vary.

Note Added in Proof: the terms mesoid and gyroid have been suggested by Professor J. H. Brewster in an alternative description of relative stereochemistry, which applies to chains where the termini are defined by priority rating or the chain name. We thank Professor Brewster for providing a copy of his manuscript.



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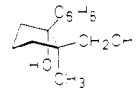
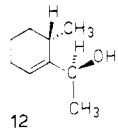


11′



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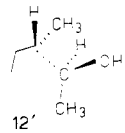
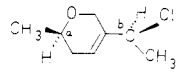


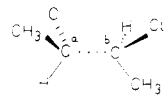
12′

higher priority one is retained as a substituent. Priority of a linking fragment is defined as the highest priority assignable in considering both of the linked centers as the origin of the link.

Consider **13**. There are two paths from a to b. The two



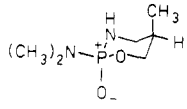
13



13′

paths from b to a include the same atoms as the two from a to b, but they differ in priority assignments at their beginning. However, the pathway a → b through oxygen is higher priority than any other, priority being established at the first point of difference on proceeding from one chiral center to the other. Therefore, **13** is treated as if it were **13′** and is pref.

Similarly, the priority pathway in **14** is from phosphorus to carbon through oxygen; **14** is treated as if it were **14′** and is the parf stereoisomer.



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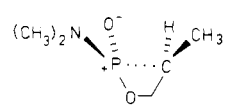
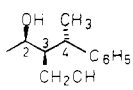


14′

Multiple Chiral Centers

The traditional descriptors for molecules that have three chiral centers are ribo, arabino, lyxo, and xylo. These are relatively unfamiliar and little used outside carbohydrate chemistry. One can apply the pref–parf system to compounds containing three or more chiral centers using the same general principles just described. All that need to be added are locants that designate the atoms whose relative configurations are at issue. Thus, **15** is 2,3-*parf*-3,4-*pref*-3-(hydroxymethyl)-4-phenyl-2-pentanol. The diastereomers of **15** are shown. They are the 2,3-parf-3,4-parf (**16**), the 2,3-pref-3,4-pref (**17**), and the 2,3-pref-3,4-parf (**18**) isomers.



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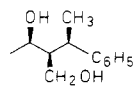

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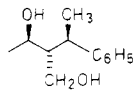

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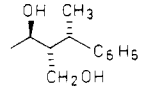

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Analysis of **15** as portrayed in Figure 4 will serve to illustrate the method. First, the relative configuration of the chiral centers C(2) and C(3) is determined in the customary way. Then, the relationship between C(3) and

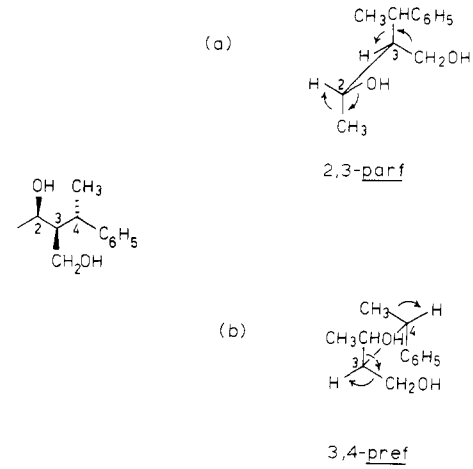
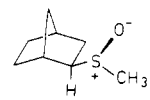


Figure 4. Identification of **15** as 2,3-*parf*-3,4-*pref*-3-(hydroxymethyl)-4-phenyl-2-pentanol. In (a), the relative configuration of C(2) compared to C(3) is determined to be parf. In (b), the C(3)–C(4) relative configuration is pref. Notice that the substituents at C(3) and their stereochemical sense differ according to whether C(3) is being related to C(2) or to C(4).

C(4) is determined independently. It is important to recognize that the substituents at C(3) differ according to whether it is the C(2)–C(3) relationship or the C(3)–C(4) relationship which is being considered. Therefore, the stereochemical sense of substitution at C(3) must be determined independently each time; one cannot carry over the stereochemical sense of C(3) used for C(2)–C(3) relative stereochemistry and apply it to C(3)–C(4) relative stereochemistry.

In some cases, it may prove convenient to use the pref and parf descriptors in conjunction with other stereochemical prefixes. Exclusive of enantiomers, there are three additional stereoisomers that have the same constitution as **19**. Compound **19** is *exo-parf*-2-(methylsulfinyl)norbornane. Its diastereomers are the endo-parf, the exo-pref, and the endo-pref isomers.



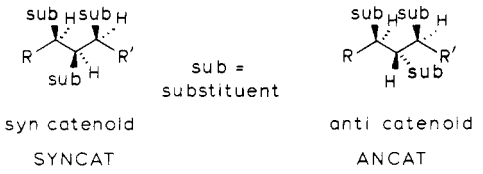
19

Informal Alternatives to Erythro and Threo and Pref and Parf

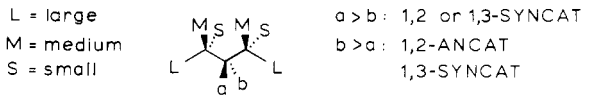
While the foregoing descriptions of relative stereochemistry at any two centers in a molecule provide an unambiguous structural definition, they do not satisfy another need of organic chemists. It is frequently desirable to have a description of relative stereochemistry that shows a stereochemical communality and that allows instant correlation of two or more molcules, where each could have diastereomeric alternatives.

With cyclic molecules this is achieved by the description of substituents as arising from either a relative cis or trans attachment to the ring system. In order to obtain an analogous description in acyclic molecules, one can, by convention, assume a chain of atoms in an extended, staggered (zig-zag) conformation.[6] If one then places subsituents along the chain and defines them as relative syn substituents if they project to the same side of the chain and as relative anti substituents if they project to opposite sides of the chain, one obtains a picture that can be directly visualized from this description. The centers at which the substituents are attached can be compared as having a relative syn catenoid (SYNCAT) or an anti catenoid (ANCAT) relationship.[14] With two substituents

at the same point in the chain, a relative weighting is, of course, required.



A description of this type is commonly required for correlation of results of stereodirected reactions, where acyclic or macrocyclic diastereomers with (more or less) one predominant relative stereochemistry are obtained. It is also useful for correlation of physical and chemical properties of such molecules. To these ends, one is primarily interested in the stereochemical properties of the chain substituents and not in their Cahn–Ingold–Prelog ratings. Thus, such a description of relative stereochemistry should be based on weighting of substituents according to steric volume (large vs. small), as commonly used in conformational analysis. In order to maximize the chemical generalizations derivable from the substituted staggered chain convention, the ends of the chain should be represented by the groups with the largest steric bulk.[15]



(14) A syn vs. anti nomenclature for substituents on a staggered chain was initially proposed by S. Masamune, SK. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew, Chem., Int. Ed. Engl.* **1980**, *19*, 557, footnote 7. If syn and anti refer to the relationships of any named *substituents*, syncat and ancat refer to the relationship of the *substituted centers, based on size of substituents*, as used in conformational analysis. We thank Professor Masamune for providing a manuscript in which a nomenclature of syn or anti is used to express relative stereochemistry of *substituted centers*, derived from *Cahn–Ingold–Prelog priorities of substituents*.

For a rigorous definition, this description can be inferior to the one given at the beginning of this paper (pref–parf) since a choice of relative group size can become ambiguous. (In such cases, it can be used in conjunction with a pref–parf specification.) However, the SYNCAT–ANCAT description will serve organic chemists in the vast majority of cases without ambiguity and, most importantly, it will allow even in verbal discussion an instant recognition of conformation and communality of chemical properties. For instance, in comparison of adjacent centers, those with noninteracting substituents that are ANCAT are always of lower energy than those with SYNCAT stereochemistry. Formation of ANCAT vs. SYNCAT centers also allows direct visualization of the relative transition-state energies leading to such products. This description of relative stereochemistry thus saves all of the useful chemical information that could be derived from the conformational analysis use of erythro vs. threo[5] without the confusion that the diverse uses of those terms have generated and with the added applicability to multiply substituted acyclic and macrocyclic molecules.

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(15) At times this may be inconvenient or ambiguous. However, there should be no confusion in any (verbal) description about which groups are the termini of a staggered chain since they will provide the name for the chain and the substituents on the chain will be listed as such by the usual chemical nomenclature.

The syncat–ancat description should be particularly useful for descriptions of multiple-substituted long chains or macrocycles where one can describe the entire stereochemistry by listing the substituent positions along the chain by numbers (a, b, c, etc.) for the majority of substituents on one side: (a, b, c, syncat), the remaining substituents at other positions along the chain are then understood to be relatively ancat derived.

Practical Multigram Syntheses of Benzocyclobutenediones

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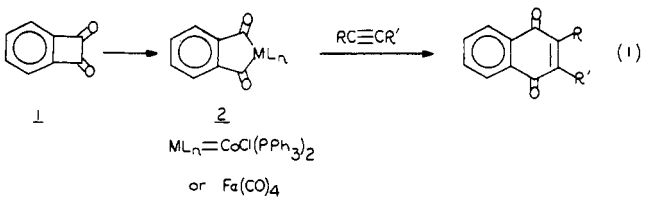
Experimentally simple syntheses of benzocyclobutenedione and substituted benzocyclobutenediones (3-OH; 4-OH; 4-Me; 3-OH, 5-Me) are described which allow the synthesis of these compounds on large scale from inexpensive starting materials. The regiospecific and stereoselective cycloaddition of trimethylsiloxy dienes to 1,4-dichloro-3,3,4-trifluorocyclobutene forms the basis of the synthesis of the substituted benzocyclobutenediones.

We recently described an organo-transition-metal approach to naphthoquinones which required benzocyclobutenedione as a starting material (eq 1).[1] The high-yield preparation of the phthaloylmetal complexes **2**[2] and the subsequent high-yield synthesis of a wide variety of substituted naphthoquinones[3] could make this a method of choice for the synthesis of functionalized naphthoquinones if two criteria can be met. Benzocyclobutenedione and substituted benzocyclobutenediones must be readily available on a multigram scale, and the substituted diones



(1) Liebeskind, L. S.; Baysdon, S. L.; South, M. S. *J. Am. Chem. Soc.* **1980**, *102*, 7397.

(2) Liebeskind, L. S.; Baysdon, S. L.; South, M. S.; Blount, J. F. *J. Organomet. Chem.* **1980**, *202*, C73.

(3) In addition to our naphthoquinone synthesis described in ref 1, we have recently prepared a stable cationic phthaloylcobalt complex which reacts with many functionalized alkynes within 2 h at 80 °C in CH_2Cl_2 to give high isolated yields of substituted naphthoquinones: Baydson, S. L.; Liebeskind, L. S. *Organometallics* **1982**, *1*, 771.

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