Diastereoselective Cyclizations of 1,3-Dioxan-2-yl Radicals: Chiral Acyl Radical Equivalents

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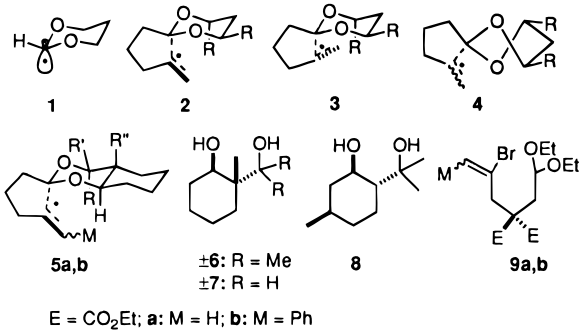
Diastereoselectivity in free radical reactions is a topic of current interest.[1] Here we introduce the concept of disymmetrically substituted 1,3-dioxan-2-yl radicals as asymmetric equivalents of acyl radicals[2] and describe their application to diastereoselective cyclizations.

The sp^3-hybridized, σ-type, 1,3-dioxan-2-yl radicals (**1**) adopt a chairlike conformation with the unpaired spin axial.[3] In this they are closely analogous to the 1-alkoxy-1-glycopyranosyl radicals which are trapped selectively from the axial direction.[4] We reasoned that 1,3-dioxan-2-yl radicals bearing an appropriate unsaturated chain at the radical center would react preferentially along the axial direction in 5-hexenyl cyclizations. Use of a C_2-symmetric system[5] would result in only two diastereomeric transition states (**2**) and (**3**), one of which (**3**) would be significantly disfavored on steric grounds. Such cyclizations should therefore be diastereoselective and, after hydrolysis, provide enantiomerically enriched α-methylcyclopentanones. Extensive experimentation, resulting in only modest ratios of diastereomers, showed this logic to be flawed. In all likelihood, the cyclizations were taking place through twist-boat conformers (**4**),[6,7] with concomitant loss of stereoselectivity, in order to minimize the 1,3-diaxial interaction between the directing group and the developing bond in **2** and **3**. The challenge therefore evolved into one of imposing a chair conformation on a disymmetrically substituted 1,3-dioxan-2-yl radical in a 5-hexenyl cyclization.

On the grounds that the rigid trans-fused bicyclic system would reduce the incidence of boat and/or twist-boat conformers, *trans*-1,3-dioxabicyclo[4.4.0]decan-2-yl transition states **5** were targeted. In **5** the substituent R is the primary stereodirecting group, R′ an artifact of the synthesis, and R″ a group intended to further disfavor boat and twist-boat conformers. The racemic diol **6** was readily synthesized from **7**[8] by selective oxidation of the primary alcohol to the corresponding aldehyde with TEMPO and NaOCl[9] and then with iodine and methanol[10] to the ester, followed by treatment with excess methylmagnesium bromide. *trans*-Menthanediol (**8**)[11,12] was selected to probe the importance of the group R″ in **5**.



Transacetalization of **9a** with **6** and **8** under standard conditions gave **10a** and **11a**, respectively. Cyclization of **10a** with 10 mol % Bu_3SnCl, 2 equiv of $NaBH_3CN$, and AIBN as initiator in benzene at reflux[13] gave 74% of an 85:15 mixture of two cyclized products (Table 1, entry 1) together with some reduced substrate. The major product was assigned the structure **12** and the minor **14a** following extensive ^{1}H-NMR and NOE studies. Clearly, **12** arises from the anticipated cyclization, depicted in **5**, followed by a rapid 1,5-abstraction of the bridgehead hydrogen from the auxiliary and eventual quenching to give the *cis*-dioxadecalin skeleton,[14] as confirmed by an experiment with Bu_3SnD (→ **13**). The minor product, which retains the *trans*-decalin skeleton and does not incorporate deuterium at the bridgehead position with Bu_3SnD, apparently arises from "equatorial" quenching of the dioxanyl radical. Under the same conditions acetal **11a** gave a more complex mixture of four cyclized products (Table 1, entry 2). The two major products were identified as **16a** and **18a**, both resulting from cyclization to radical **20**, followed by hydrogen atom abstraction to **21** and quenching of the bridgehead radical from either face, again confirmed with Bu_3SnD (→ **17a** and **19**). The two unresolved minor products, which incorporated deuterium into the methyl group with Bu_3SnD, were assigned as the two isomers **22a**. Evidently, the axial substituent (R″ in **5**) has a distinct effect on both the

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(1) Reviews: (a) Smadja, W. *Synlett.* **1994**, 1. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.
(2) Lead references to acyl radicals: (a) Crich, D.; Chen, C.; Hwang, J.-T.; Yuan, H.; Papadatos, A.; Walter, R. I. *J. Am. Chem. Soc.* **1994**, *116*, 8937. Reviews: (b) Nájera, C.; Yus, M. *Org. Prep. Proc. Int.* **1995**, *27*, 383.
(3) (a) Malatesta, V.; McKelvey, R. D.; Babcock, B. W.; Ingold, K. U. *J. Org. Chem.* **1979**, *44*, 1872. (b) Malatesta, V. Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609. (c) Gregory, A. R.; Malatesta, V. *J. Org. Chem.* **1980**, *45*, 122. (d) Hayday, K.; McKelvey, R. D. *J. Org. Chem.* **1976**, *41*, 2222. (e) Beckwith, A. L. J.; Easton, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 615. (f) Beckwith, A. L. J.; Brumby, S. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1801.
(4) Lead references: (a) Crich, D.; Sun, S.; Brunckova *J. Org. Chem.* **1996**, *61*, 605. (b) Yamazaki, N.; Eichenberger, E. Curran, D. P. *Tetrahedron Lett.* **1994**, *35*, 6623. (c) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716. (d) Sugai, T.; Shen, G.-J.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 413.
(5) Reviews: (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (b) Alexakis, A.; Manganey, P. *Tetrahedron Asym.* **1990**, *1*, 477.
(6) *trans*-4,6-Disubstituted 2,2-dimethyl-1,3-dioxanes adopt twist-boat conformations: (a) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511. (b) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251.
(7) Conformational analysis of 1,3-dioxanes: Anteunis, M. J. O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4*, 293.
(8) Smith, W. B. *J. Org. Chem.* **1979**, *44*, 1631.
(9) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.
(10) Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. C* **1968**, 1693.
(11) Aldrich Chemical Co., Milwaukee, WI.
(12) Asakawa, Y.; Mutsuda, R.; Tori, M.; Hashimoto, T. *Phytochemistry* **1988**, *27*, 3861.
(13) (a) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (b) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051. (c) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900.
(14) For the stereochemistry of quenching of simple 9-decalinyl radicals with tin hydrides see: Greene, F. D.; Lowry, N. N. *J. Org. Chem.* **1967**, *32*, 882.

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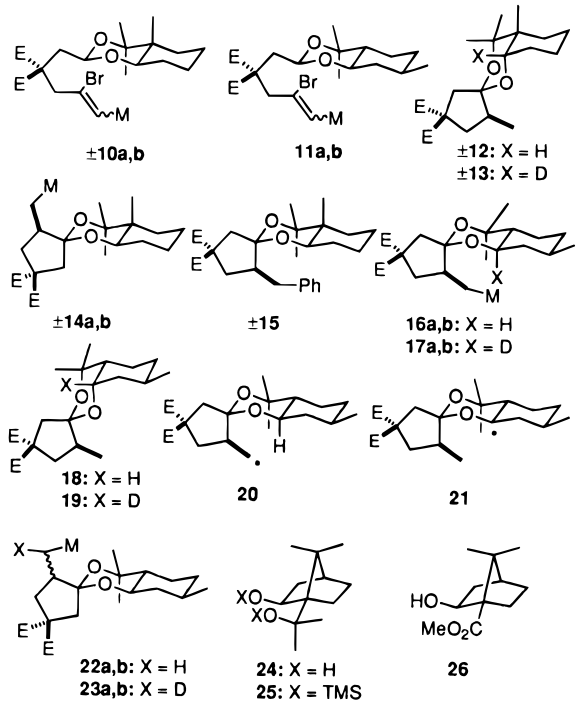
Table 1. Diastereoselective Cyclizations

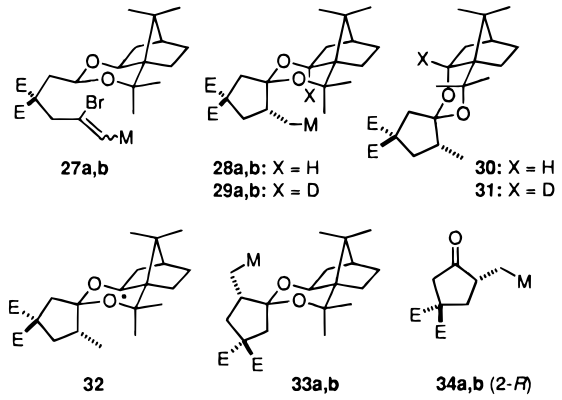
entry	substrate	*T* (°C)	% yield of cyclized product	ratio of cyclized products	ketone (% ee)
1	**(±)-10a**	80	74	**12:14a** = 85:15	
2	**11a**	80	72	**16a:18:22**[a] = 40:30:30	**34a** (52)
3	**27a**	80	74	**28a:30:33a** = 84:11:5	**34a** (78)
4	**27a**	20	51	**28a:30** = 87:13	**34a** (95)
5	**(±)-10b**	80	64	**14b:15** = 35:65	
6	**11b**	80	65	**16b:22b**[a] = 73:27	**34b** (42)
7	**27b**	80	50	**28b:33b** = 80:20	**34b** (38)
8	**27b**	20	29	**28b:33b** = 94:6	**34b** (62)

[a] **22a** and **22b** were ≃1:1 mixtures of diastereomers.

cyclization stereochemistry and on the quenching of any bridgehead radicals generated subsequent to cyclization.[15]



Diol **24** was selected as an enantiomerically pure equivalent of **6**.[16] It was readily available from **26**,[17] itself obtained from ketopinic acid,[18] by treatment of the TBDMS ether with MeLi and then $Bu_4N^+F^-$. Acetalization of **24** was achieved by reaction of **25** with the aldehyde corresponding to **9a** catalyzed by TMSOTf,[19] when crystalline **27a** could be obtained in good yield. Cyclization of **27a** under the standard conditions gave 74% of a mixture of three cyclized products (Table 1, entry 3). The two major products, **28a** and **30**, arise from the preferred cyclization followed by *δ*-hydrogen abstraction to **32** and subsequent nonselective quenching, as was confirmed by an experiment with Bu_3SnD resulting in the formation of **29a** and **31**. The minor product (**33a**), which does not incorporate deuterium into the bornane framework in the presence of Bu_3SnD, again arises from cyclization on the exo-face. When the cyclization was conducted with Bu_3SnH photochemically at 20 °C only two cyclization products, **28a** and **30**, both arising from the one preferred mode of cyclization, were found (Table 1, entry 4).



For the acetals **10b**, **11b**, and **27b** interpretation was simplified owing to the suppression of the second hydrogen atom abstraction by benzylic stabilization of the cyclized radicals. Nevertheless, cyclization diastereoselectivities were somewhat lower (Table 1, entries 5−8), an observation which is tentatively attributed to increased 1,3-diaxial interactions in **5** narrowing the energy gap between it and the twist-boat. However, it was again noted that operating at the lower temperature (Table 1, entry 8) increased selectivity substantially.

Hydrolysis of the cyclized products was best achieved with catalytic $Pd(Cl)_2(CH_3CN)_2$ in acetone.[20] The ee's of the resulting ketones were determined by ^{1}H-NMR spectroscopy in the presence of (*S*)-1-(9-anthracenyl)-3,3,3-trifluoroethanol (Table 1, entries 2−4 and 6−8).[21,22] In agreement with the mechanistic rationale, hydrolysis of a mixture of **28a**, **30**, and **33a** gave **34** highly enriched in the (+)-enantiomer with a negative Cotton effect in the CD spectrum consistent with the *R*-configuration (Table 1, entry 3), while that of a mixture of **16**, **18**, and **22** gave **34** enriched in the (−)-enantiomer (Table 1, entry 2).[23]

The above results augur well for the use of **24** as a chiral auxiliary in diastereoselective radical cyclizations; further progress will be reported in due course.

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Supporting Information Available: Lists of characterization data for (±)-**6**, (±)-**10ab**, **11ab**, **24**, **25**, **27ab**, **34ab**, and the mixtures of **12** with **14a**, **16a** and **18** with **22a**, **28a** with **30a**, **14b** with **15**, **16b** with **22b**, and **28b** with **33b**. Copies of ^{1}H-NMR spectra of (±)-**10b**, **11b**, and **27b** and of the cyclized products for Table 1, entries 1−8 (14 pages).

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(15) The two alkyl groups R′ and R″ (**5**) in **10** and **27** severely restrict the number of boat and twist boat conformers resulting in formation of only one isomer (**14** and **33**) from exo-face quenching as opposed to the mixture (**22**) obtained when R′ = H as in **11**.

(16) The basic structural motif could be obtained from selected terpenoids such as hederagenin and aphidicolin, but their relative inaccessibility renders them unattractive for use as chiral auxiliaries.

(17) (a) Ishizuka, T.; Kimura, K.; Ishibuchi, S.; Kunieda, T. *Chem. Pharm. Bull.* **1990**, *38*, 1717. (b) Ishizuka, T.; Ishibuchi, S.; Kunieda, T., *Tetrahedron Lett.* **1989**, *30*, 3449.

(18) Bartlett, P. D.; Knox, L. H. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. V, p 689.

(19) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(20) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.

(21) Chiral lanthanide shift reagents were unsatisfactory.

(22) Although the Pirkle solvating agent is usually applied to more polar species, NMR resolution of simple lactones has been reported: (a) Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384. (b) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1978**, *43*, 378.

(23) The ee of the free ketones, in each case, is lower than that calculated from the mixtures of acetals used. Some racemization is occuring in the hydrolysis. Numerous conditions were assayed, and the use of $Pd(Cl)_2(CH_3CN)_2$ in acetone was found to minimize this problem.