lyzed rates for the peptides, indicating that FKBP is exercising specificity as a catalyst and not nonspecifically enhancing the uncatalyzed process for each peptide. Moreover, there is no evident trend among the enzymatic rates and the equilibrium constant of the two rotamers for each peptide (data not shown), indicating that the differences in enzymatic rates are not simply a reflection of the relative abundance of the cis peptide.

The rank order of this series of peptides is fully consistent with the aforementioned hypothesis regarding the nature of binding of FKBP by FK506 and rapamycin as twisted amide surrogates. The fact that predictions made from the structures of these inhibitors about the substrate specificity of the rotamase activity were upheld argues that the binding site of FK506 and rapamycin and the active site of the rotamase activity of FKBP are identical, i.e., FK506 and rapamycin are competitive inhibitors of the rotamase activity of FKBP—an issue which cannot be addressed directly due to limitations of the current assay. These results corroborate our view of FK506 and rapamycin as transition-state analogues for amide rotation by FKBP and extend the region of molecular recognition into the S1 site of FKBP. We conclude that the potent inhibition (e.g., K_i(rapamycin) = 2.0×10^{-10} M)[13] of the rotamase activity by these structures is in part due to the complementary topographical relationship between the binding site of FKBP and the immunosuppressive agents FK506 and rapamycin, which act as leucine–(twisted amide)–proline surrogates (Figure 3).

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Asymmetric Cyclopropanation of 1-Alkenylboronic Esters and Its Application to the Synthesis of Optically Active Cyclopropanols

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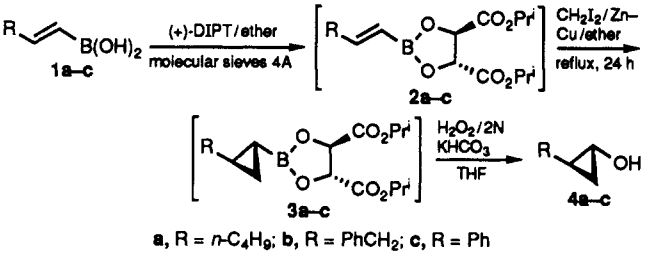
Summary: The first asymmetric cyclopropanation of 1-alkenylboronic esters was realized by diastereofacial selective Simmons–Smith reaction of the esters modified by enantiomerically pure diols such as tetramethyltartaramide. Subsequent oxidation of the resulting cyclopropylboronates gave optically active 2-substituted cyclopropanols in 73–94% ee. These reactive compounds possess high synthetic potential.

We report herein the asymmetric cyclopropanation of 1-alkenylboronic esters to the corresponding cyclopropylboronic esters, which, on subsequent oxidation, afford 2-substituted cyclopropanols of high optical purity.[1,2] To our knowledge, this is the first example of diastereofacial selection in enantiomerically pure 1-alkenylboronic esters.[3] Since the optically active cyclopropylboronic esters as well as the resultant cyclopropanols[4] could serve as versatile intermediates in enantioselective synthesis, the present, simple method for preparing these compounds should be of considerable value in synthetic organic chemistry.

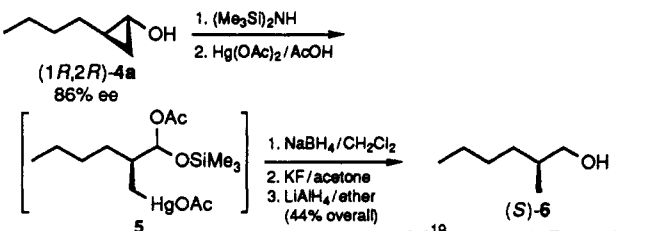
Recently, two new methods for preparing optically active cyclopropanols by asymmetric cyclopropanation of enol ether derivatives have appeared.[5,6] Although one of them has achieved a very high level of asymmetric induction, the types of cyclopropanols prepared are rather limited (mainly bicyclic tertiary alcohols).[5b] Our new method enables access to a different type of cyclopropanol (secondary ones bearing a vicinal substituent). These methods may, thus, be complementary for preparing this important class of compounds with various substitution patterns.

Scheme I



a, R = *n*-C_4H_9; **b**, R = $PhCH_2$; **c**, R = Ph

Scheme II



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0022-3263/90/1955-4986$02.50/0

Table I. Asymmetric Cyclopropanation of 1-Alkenylboronic Esters and Direct Oxidation to Optically Active Cyclopropanols[a]

alkenylboronic acid (R =)	chiral diol[b]	cyclopropanol[c]	specific rotation (concentration, solvent)	yield,[d] %	ee,[e] %
1a (*n*-butyl)	(+)-DMT	(1*R*,2*R*)-**4a**	$[\alpha]^{22}_D$ -42.7° (*c* 0.658, EtOH)	41	73
1a	(+)-DIPT	(1*R*,2*R*)-**4a**	$[\alpha]^{21}_D$ -49.2° (*c* 1.16, $CHCl_3$)	44[f]	86
1a	(+)-TMTA	(1*R*,2*R*)-**4a**	$[\alpha]^{21}_D$ -56.3° (*c* 0.741, EtOH)	48	93
1a	(+)-TMTA	(1*R*,2*R*)-**4a**	$[\alpha]^{22}_D$ -54.0° (*c* 0.879, EtOH)	67[g]	91
1a	(+)-TMTA	(1*R*,2*R*)-**4a**	$[\alpha]^{22}_D$ -56.3° (*c* 0.678, EtOH)	67[g,h]	94
1a	(−)-TMTA	(1*S*,2*S*)-**4a**	$[\alpha]^{22}_D$ +54.1° (*c* 0.861, EtOH)	42	90
1b (benzyl)	(+)-DIPT	(1*R*,2*R*)-**4b**	$[\alpha]^{23}_D$ -27.2° (*c* 0.623, EtOH)	57[f]	81
1b	(+)-TMTA	(1*R*,2*R*)-**4b**	$[\alpha]^{22}_D$ -30.2° (*c* 0.780, EtOH)	61	89
1c (phenyl)	(+)-DIPT	(1*R*,2*S*)-**4c**	$[\alpha]^{24}_D$ -62.2° (*c* 0.629, EtOH)	60	73
1c	(+)-TMTA	(1*R*,2*S*)-**4c**	$[\alpha]^{27}_D$ -79.9° (*c* 0.512, EtOH)	46	91

[a] The cyclopropanation was performed by refluxing a mixture of 1 (2 mmol), CH_2I_2 (6 mmol) and Zn–Cu (1.2 g) in ether (7 mL) with magnetic stirring for 24 h, unless otherwise noted. [b] DMT = dimethyl tartrate; DIPT = diisopropyl tartrate; TMTA = *N,N,N′,N′*-tetramethyltartaramide. [c] The absolute configurations were determined by chemical correlation method (see the text). [d] Yield for the distilled pure product. [e] Estimated by capillary GC for its MTPA ester. [f] Performed in 9-mmol scale. [g] The Simmons–Smith reaction was performed at room temperature for 5 h. [h] Performed in 20-mmol scale.

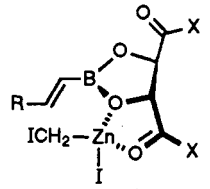
The merits of our approach are (i) easy access to the stereodefined starting 1-alkenylboronic acids or esters,[7] (ii) facility of modifying these compounds by a variety of optically active diols,[3,8] (iii) attainment of a high degree of asymmetric induction by employing inexpensive tartaric acid derivatives as the chiral modifier, and (iv) the synthetic potential of the intermediate cyclopropylboronates for which various transformations other than simple oxidation are possible.[3,8]

For the present purposes, the original Simmons–Smith procedure[9] was found to give good results. Thus, as depicted in Scheme I, *trans*-1-hexenylboronic acid (**1a**)[10] was first esterified with 1 equiv of (+)-diisopropyl tartrate (DIPT) in ether in the presence of 4-Å molecular sieves (or by azeotropic removal of water with 1,2-dichloroethane), and the ester was reacted in refluxing ether for 24 h with the Simmons–Smith reagent prepared from 3 equiv of methylene iodide and a large excess of Zn–Cu couple.[9,11] After filtering the excess metal and washing the filtrate with saturated aqueous NH_4Cl, the crude cyclopropylboronate obtained was directly oxidized in tetrahydrofuran with 3 equiv of 30% H_2O_2 and 2 N aqueous $KHCO_3$ at room temperature for 2 h to give *trans*-(−)-2-butyl-1-cyclopropanol (**4a**),[12] which was isolated by flash chromatography and distillation in 44% overall yield. Capillary GC analysis of its α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester indicated that the cyclopropanol had been formed in 86% enantiomeric excess (ee). The absolute configuration was found to be 1*R*,2*R* by chemical conversion to (*S*)-(−)-2-methyl-1-hexanol (**6**)[13] via ring opening with mercury(II) acetate[14] as shown in Scheme II.

Use of (+)-*N,N,N′,N′*-tetramethyltartaramide (TMTA) in place of (+)-DIPT made slight improvement in the degree of asymmetric induction, while (+)-dimethyl tartrate (DMT) gave somewhat poorer results (Table I).

Under these conditions, ((*E*)-3-phenyl-1-propenyl)boronic acid (**1b**)[10a,12] and ((*E*)-2-phenyl-1-ethenyl)boronic acid (**1c**)[15] were also cyclopropanated in the same stereochemical sense to give, after the oxidation, (1*R*,2*R*)-(−)-2-benzyl-1-cyclopropanol (**4b**)[12] and (1*R*,2*S*)-(−)-2-phenyl-1-cyclopropanol (**4c**),[12,16] respectively, with nearly the same level of asymmetric induction (Table I). By a similar sequence to that illustrated in Scheme II, (−)-**4b** and (−)-**4c** were converted to (*S*)-(+)-2-methyl-3-phenylpropanal (**7**)[17] (without the $LiAlH_4$ reduction in this case), and (*S*)-(−)-2-phenyl-1-propanol (**8**),[18] respectively. Alcohol **4c** solidified at room temperature, and its enantiomeric purity could be easily upgraded by simple recrystallizations from a mixture of pentane and a small amount of ether, mp 54.5–59.5 °C (lit.[16] mp 41.5–42 °C), $[\alpha]^{26}_D$ -86.3° (*c* 0.694, ethanol), 99.9% ee (by the capillary GC method).

The observed diastereofacial selectivity can be rationalized by assuming chelation of the Simmons–Smith reagent by the substrate prior to the methylene transfer as depicted in model **9**.[19]



9: X = OMe, OPr^i, or NMe_2

Finally, to demonstrate the synthetic potential of the intermediate optically active cyclopropylboronates, we converted the crude ((1*R*,2*R*)-2-butyl-1-cyclopropyl)boronic acid (**10**) to ((1*R*,2*R*)-2-butyl-1-cyclopropyl)methanol (**11**)[12,20] [bp (bath temperature) 105–115 °C (12 Torr); $[\alpha]^{19}_D$ -33.1° (*c* 0.558, ethanol)] in 52% overall yield by the following sequence: (i) esterification with 1,3-

(7) Although, in this communication, only terminal (*E*)-1-alkenylboronic esters were studied because of their availability by hydroboration of terminal alkynes, preparative methods for alkenylboronic esters of almost any structural types have already been developed (ref 8a,b).

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(11) The reaction conditions have not been fully optimized, but it has been found, in one case, that the reaction proceeds at a reasonable rate and more cleanly at room temperature (see Table I).

(12) The structure is consistent with its ^{1}H NMR and IR spectral properties as well as elemental analysis.

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propanediol, (ii) Matteson's one-carbon homologation reaction (CH_2ClI/n-BuLi),[21] and (iii) oxidation (30% H_2O_2/2 N $KHCO_3$). The cyclopropylmethanol **11**, in turn, can be ring opened to *threo*-2-methyl-1,3-heptandiol in a regioselective and stereospecific manner,[20] the above conversion shows one way to extend the utility of this method in enantioselective organic synthesis.

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Acknowledgment. We thank the Ministry of Education, Science, and Culture, Japan, for financial support to this work (Grant-in-Aid for Scientific Research, No. 02640374).

Supplementary Material Available: Representative procedures for the cyclopropanation of **1a–c**, the ring opening of **4a–c**, and the homologation of **10** and the spectral and physical properties as well as the analytical data of **1b**, **4a–c**, **6–8**, and **11** (6 pages). Ordering information is given on any current masthead page.

A Novel Oxidative Skeleton Rearrangement of the Caffeine System

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Summary: 8-(Disubstituted amino)- and 8-alkoxycaffeines react with 3-chloroperoxybenzoic acid to undergo a novel rearrangement giving spiro compounds of type **5**.

We report here on results of a peroxy acid oxidation of 8-(*N,N*-disubstituted amino)caffeines (systematic names: 8-(*N,N*-disubstituted amino)-3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-diones), **1**, and the related compounds **2**. Our initial objective in this area[1,2] was the synthesis of their *N*-oxide analogues as potential antitumor agents. Procedures for the synthesis of a number of purine *N*-oxides have been reported previously by several authors.[3-13] In particular, the preparation of several purine *N*-oxides by direct oxidation of the parent bases was first reported by von Euler[3] as well as by Brown.[4,5]

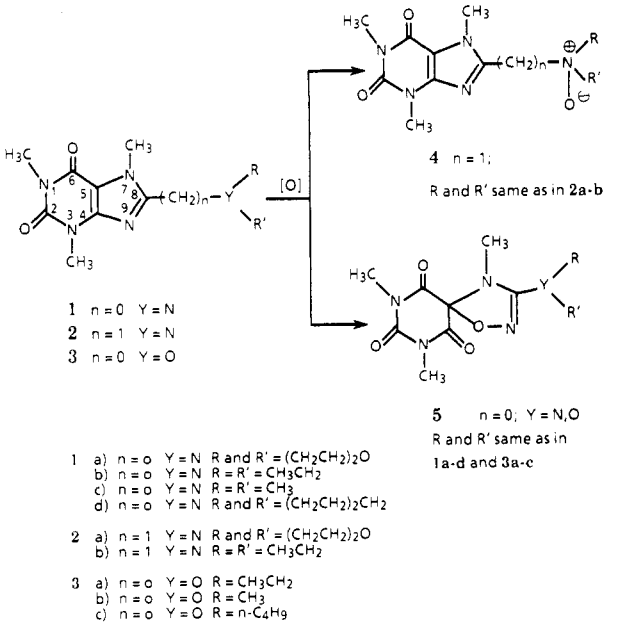
Based on literature precedent,[14] we envisioned that peracid oxidation of **1** with an amino function in the 8-position would yield *N*-oxides of type **4**. Instead, when type **1** compounds were treated with 3-chloroperoxybenzoic acid in a chloroform–water mixture, lemon-yellow products **5** were obtained in good yields (Table I). The elemental analyses and mass spectral data of these species showed that they possess two oxygen atoms more than the type **1** pecursors. ^1H and ^{13}C NMR spectral data of **5** showed symmetry in these products. Thus, in the ^1H NMR spectrum of **5a** the two singlets due to the *N*-CH_3 groups of the pyrimidine ring merged into one singlet. The decoupled ^{13}C NMR spectrum (75.5 MHz) of **1a** exhibits 10 singlets at δ 27.563, 29.510, 32.356, 49.868, 66.256, 104.972, 146.969, 151.262, 154.432, and 155.632 corresponding to N_7-CH_3, N_3-CH_3, N_1-CH_3, $C_{10,10'}$, $C_{11,11'}$, C_8, C_4, C_5, C_6, and C_2 respectively, while the decoupled ^{13}C NMR spectrum of **5a** shows only seven singlets at δ 29.440, 49.360, 65.948, 91.233, 149.864, 160.964, and 164.463. These data could

Table I. 3-(*N,N*-Disubstituted amino)-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4.5]dec-2-ene-6,8,10-triones and Their 3-Alkoxy Analogues[27]

compd	Y	R	R′	mp,[a] °C (uncorr)	yield, % (isolated)
5a	N	$-(CH_2CH_2)_2O$		224	61
5b	N	CH_3CH_2	CH_3CH_2	135	57
5c	N	CH_3	CH_3	149	33
5d	N	$-(CH_2CH_2)_2CH_2$		176	51
5e	O	CH_3CH_2	–	176	41
5f	O	CH_3	–	188	58
5g	O	n-C_4H_9	–	158	27

[a] Recrystallized from ethanol.

Scheme I



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