mainly because of the observation that tetrazoles are common byproducts of the Schmidt reaction (resulting from the reaction of c with another molecule of hydrazoic acid), but also because azides did not react under conditions similar to those employing hydrazoic acid.[2] Thus, it was hypothesized that path B had to be operative because the formation of b was not possible when R ≠ H. Reactions in which tetrazoles are not observed may be explained by invoking path A; for example, regiochemical differences,[8,10] the dependence of products obtained under conditions of varying acid strength,[9] and the obtention of amides from reactions of alkyl azides with benzaldehyde but not with various ketones[2c,11] have been explained by invoking changes in mechanism. Our previous paper[7] and the present disclosure show unambiguously that intermediates similar to a (R = alkyl) can directly rearrange via path A to the corresponding amide under appropriate conditions.

In conclusion, we have shown that some ketones undergo $TiCl_4$-catalyzed Schmidt reactions with alkyl azides to give N-substituted lactams in synthetically useful yields. Furthermore, we have demonstrated that, in some cases, the Schmidt reaction of simple ketones can proceed by direct rearrangement of an azidohydrin intermediate.

Acknowledgment. This work was supported by the National Institutes of Health. J.A. acknowledges an Eli Lilly Granteeship (1989–1991). C.J.M. is the recipient of a National Institutes of Health predoctoral fellowship.

Supplementary Material Available: Representative experimental procedures for preparation of azides and rearrangement reactions, spectral data, and ^1H and ^{13}C NMR spectra (51 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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A Highly Convergent Asymmetric Synthesis of the C(19)–C(27) Segment of Rifamycin S: An Application of Enantiodifferentiating Acetalization with Menthone

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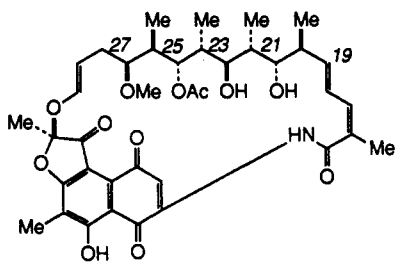
Summary: An enantiodifferentiating transformation of 1,3-alkanediols by kinetic acetalization with menthone is developed and used in a highly convergent asymmetric synthesis of the C(19)–C(27) segment of the ansa chain of rifamycin S.

Rifamycin S (1) is a well-known member of the ansamycin antibiotic group.[1] Following the landmark total synthesis reported by Kishi and co-workers in 1980,[2] much effort has been directed toward the synthesis of the stereochemically rich ansa chain and, thereby, toward the development of effective means of controlling contiguous stereogenic centers.[3,4] We report here a highly convergent asymmetric synthesis of the C(19)–C(27) segment **13** that utilizes two-direction chain synthesis[5] (Scheme I). Crucial terminus differentiation of σ-symmetric intermediate **8** was enantioselectively achieved by using a novel, kinetic acetalization with *d*-menthone.



1

The symmetric sequence of seven contiguous stereogenic centers in the C(19)–C(27) segment was constructed efficiently in three steps from dialkenyl carbinol derivative **2**. Double hydroboration of **2** with 9-BBN furnished diol **3** with high stereoselectivity (anti,anti:anti,syn = 13:1).[6] Swern oxidation[7] of **3** afforded the corresponding di-

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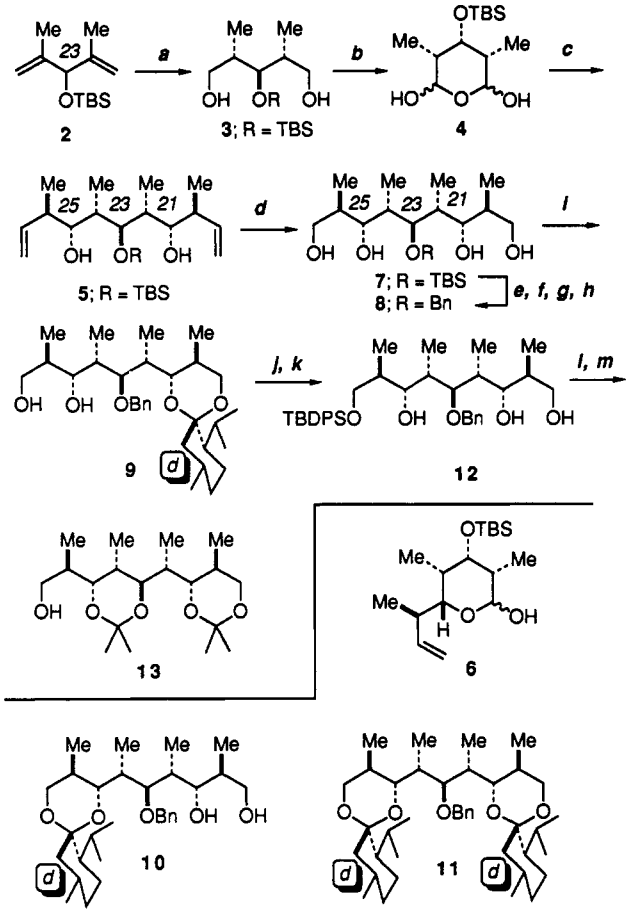
Table I. Stereoselective Acetalization of 14a with Menthone[a]

entry	substrate[b]	menthone[b]	acid[b]	solvent	time (h)	15a:16a[c]	yield (%)
1	bis-TMS of **14a** (1.0)	*dl*- (2.0)	TMSOTf (0.2)	CH_2Cl_2	18	1:5.4	99
2	bis-TMS of **14a** (1.0)	*dl*- (2.0)	TMSOTf (0.2)	CH_2Cl_2	2	1:1.6	20
3	**14a** (2.0)	*l*- (1.0)	TfOH (0.4)	CH_2Cl_2	2	3.5:1	16
4[d]	**14a** (2.0)	*l*- (1.0)	TfOH (0.4)	CH_2Cl_2	5	2.4:1	59
5[e]	bis-TMS of **14a** (2.0)	*l*- (1.0)	TfOH (0.2)	CH_2Cl_2	2.5	6.6:1	63
6[e]	bis-TMS of **14a** (2.0)	*l*- (1.0)	TfOH (0.2)	THF	1.5	10:1	88
7	**14a** (1.0)	**17** (1.0)	TfOH (0.1)	THF	1.5	9.3:1	51

[a] All reactions were performed at −40 °C under argon atmosphere. [b] The value in parentheses indicates the equivalent of a reagent (or substrate). [c] Determined by capillary GC analysis (30 m, PEG-20M). [d] 4A Sieves were added. [e] After treatment of the bis-TMS ether with 0.5 equiv of H_2O in the presence of TfOH at 0 °C for 2 h, *l*-menthone was added to the resulting mixture at −40 °C.

Scheme I[a]



[a] (a) 9-BBN (3.0 equiv), THF, −85 to 0 °C; NaOOH (anti,anti: anti,syn = 13:1, 93%); (b) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (c) pinacol (*E*)-crotylboronate (6 equiv), 4A sieves, 40 °C, 25 h, and then 100 °C, 3.5 days (**5**; 53% (overall yield from **3**), stereoisomers of **5**; 7%, and **6**; 8%); (d) ozone, MeOH; Me_2S; $NaBH_4$ (79%); (e) $Me_2C(OMe)_2$, CSA; (f) *n*-Bu_4NF, THF (79% in two steps); (g) BnBr, NaH, THF–DMF (99%); (h) aq HOAc (80%); (i) *d*-menthone enol TMS ether (2.0 equiv), TfOH (0.2 equiv), THF, −40 °C, 2 h (**9** + **10**, 4.5:1, 61%; **11**, 12%; **8**, 10%); (j) TBDPSCl (3 equiv), imidazole (3 equiv), DMF (68%); (k) $CHCl_3$ saturated with 9 N HCl, rt (85%); (l) Pd/C (10%), H_2, EtOH; (73%); (m) e and then f (63% in two steps).

aldehyde as its cyclic hydrate **4**, whose ^{1}H-NMR spectrum ($CDCl_3$) revealed that the hydrate is in equilibrium with the dialdehyde in solution. The remaining four stereogenic centers were convergently introduced by double crotylboration[8] of the dialdehyde. Reaction of **4** with achiral pinacol (*E*)-crotylboronate (6 equiv) (developed by Roush[9]) in the presence of 4A sieves gave bis-adduct **5**[10] (53%) as a pure crystalline solid (mp 81 °C) together with the stereoisomers of **5** (7%) and monoadduct **6** (8%). Ozonolysis of **5** followed by $NaBH_4$ reduction yielded tetrol **7**. In order to avoid the participation of the TBSO group in subsequent enantiodifferentiating transformations,[11] **7** was converted into benzyl derivative **8** in 4 steps.[12]

We recently disclosed that acetalization of racemic 1,3-alkanediols *rac*-**14** with *l*-menthone proceeds stereoselectively at the resulting dioxy carbon to give, from among four possible diastereomers, **15** (derived from **14**) and **16** (derived from *ent*-**14**) in a 1:1 ratio.[13,14] So, the crucial enantiodifferentiating transformation of tetraol **8** would be achievable if there were a significant difference in rate of the acetalization with menthone between the terminal (21*S*)- and (25*R*)-1,3-diol moieties in **8**. The potential of the kinetic enantiodifferentiation was examined in a model study of the racemic diol **14a** (R^1, R^2 = $-(CH_2)_5-$, R^3 = Me) (Table I).

Reaction of the bis-TMS ether of *rac*-**14a** with *dl*-menthone, catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf),[14] yielded an equilibrium mixture of **15a** and **16a** in which the thermodynamically more stable acetal **16a** predominated (entry 1).[15] No selectivity was observed in the early, kinetic phase of the reaction (entry 2). In contrast, triflic acid-catalyzed condensation of diol *rac*-**14a** with *l*-menthone resulted in the preferential formation of **15a** though the reaction did not go to completion (entry 3). Addition of 4A sieves improved the yield but lowered the selectivity for the kinetic product **15a**, probably due to the competing isomerization to the thermodynamic product **16a** (entry 4). Partial hydrolysis of the bis-TMS derivative with 0.5 equiv of H_2O in the presence of triflic acid, followed by treatment of the resulting mixture[16] with *l*-menthone, leads to a smooth acetalization to afford **15a** with high stereoselectivity (entries 5 and 6).

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(10) The spectroscopic properties (^{1}H NMR, IR, mass spectrum, and/or HRMS) of all new compounds are fully consistent with the assigned structures.
(11) TMSOTf-catalyzed acetalization of tetrakis-TMS ether of **7** with *l*-menthone (CH_2Cl_2, −10 °C, 48 h, and then aqueous NaOH/EtOH, rt) resulted in selective formation (4.0:1) of the corresponding 21,23-(or 23,25-)menthonide in 53% yield whose absolute configuration was not determined.
(12) Benzyl ether **8** can also be prepared from the benzyl analogue of **2** by a reaction sequence similar to that for TBS ether **7** (i.e., a, b, c, and d in Scheme I). This route was less satisfactory for a multigram-scale synthesis because of difficulties in separation of stereoisomers produced in the hydroboration and crotylboration.
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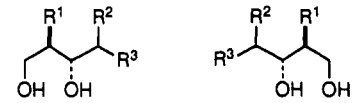
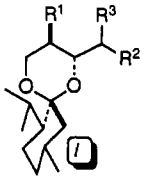
(16) The mixture contains the mono-TMS ethers (secondary/primary OH (10:1)), bis-TMS ether, and diol in a ratio of 78:11:11 (entry 5).

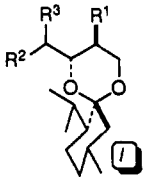


14 (14a; R¹ = Me, R², R³ = -(CH₂)₅-)

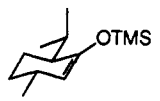
ent-14



15 (15a; R¹ = Me, R², R³ = -(CH₂)₅-)



16 (16a; R¹ = Me, R², R³ = -(CH₂)₅-)



17

More conveniently, kinetic acetalization was accomplished by treating the diol with *l*-menthone enol silyl ether (17) in the presence of triflic acid in THF (entry 7).[17] Formation of $(TMS)_2O$ may account for the facile, kinetic acetalization under these conditions.

The enantiodifferentiating transformation of *meso*-tetrol 8 was achieved successfully by employing the kinetic acetalization with *d*-menthone.[18] Treatment of 8 with 2 equiv of *d*-menthone enol TMS ether in the presence of TfOH (0.2 equiv) in THF at −40 °C for 2 h afforded a 4.5:1 mixture of menthonides 9 and 10 (61%) together with bis-menthonide 11 (12%) and recovered tetrol (10%).[19] Conversion of the mixture of 9 and 10 to the bis-TMS derivatives followed by separation by flash chromatography and subsequent desilylation gave pure 9 (mp 129–131 °C) (72%).

Selective protection of the primary hydroxy group of 9 as the TBDPS ether and subsequent hydrolysis of the menthonide gave triol 12. Finally, debenzylation followed by protection of the tetrol as its bis-acetonide and subsequent desilylation afforded 13 ($[\alpha]_D^{25}$ −5.07° (*c* 1.10, $CHCl_3$), >95% ee[20]), an intermediate in Kishi's synthesis of rifamycin S which had ^{1}H-NMR and specific rotation data in agreement with those reported previously.[2c,3k,l]

The studies reported herein not only serve as an illustration of the potential of the two-directional chain synthesis but also provide a new method for the enantiodifferentiating transformation of 1,3-polyols utilizing kinetically controlled acetalization with menthone.

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Supplementary Material Available: Experimental details and spectral data for 4, 5, 7, 8, 9, 12, and 13 (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) In this reaction, (*R*)-14a of 70% ee was recovered in 44% yield.
(18) Acetalization of tetrakis-TMS ether of 8 with *l*-menthone under thermodynamic conditions (TMSOTf (0.3 equiv), toluene, −30 °C, 7 days) afforded a 53% yield of 9 and 10 in a 2.0:1 ratio.
(19) Higher selectivity (6.5:1) for 9 was observed in the lower conversion (51%) of 8.
(20) The value was determined by ^{1}H NMR analysis of (+)-MTPA ester of 13.

Transmission of Recognition Information to Other Sites in a Molecule: Proximity of Two Remote Sites in the Spirobenzopyran by Recognition of Alkali-Metal Cations

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Summary: A new spirobenzopyran was synthesized, in which recognition of alkali-metal cations induced a structural change in the molecule accompanying coloration that resulted in a proximity of two remote sites in the molecule.

We report an advanced artificial receptor in which recognition induces a structural change in the molecule accompanying coloration that results in a proximity of two remote sites in the molecules. Transmission of recognition information to other sites in the molecules is crucial in many biological systems,[1] such as enzyme and nervous systems, so that mimic of the process using simple and artificial molecules may be a worthwhile subject in its own right.

Our strategy utilizes the fact that isomerization of the spirobenzopyrans possessing a monoaza-crown ring as a recognition site to the open colored merocyanines is induced by recognition of alkali-metal cations.[2] We expected that the isomerization of a rationally designed new spirobenzopyran (1a) possessing a monoaza-crown ether, propynyl, and indane groups might have propynyl-Me groups approach the π-electrons of the indane–benzene ring, and any change in the microscopic environment of the Me groups could be easily detected by NMR (Scheme I). This new type of receptor is different from the artificial

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