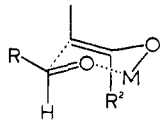
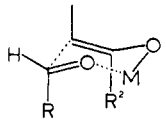
formation of Z-enolates. This last finding is general for a variety of simple ketones and obviously has great synthetic utility.

Aldol Reaction of 4 with a Lithium Z-Enolate. The 3-hydroxy-2-methylcarboxylic acid esters corresponding to **4a–e** (see Scheme II) are prepared according to known procedures (Table II) in either optically active or racemic form and then are converted to the aldehydes **4a–e** in the usual fashion. The aldol reaction with the Z-enolate generated with **12** proceeds efficiently (<5 min) at −78 °C to provide two major products, **8** and **9**,[10c] in 70–90% yield in addition to minor 2,3-anti stereoisomers corresponding to **8** and **9**. The amounts of these 2,3-anti isomers are significantly smaller[10d] than those observed in the aldol reaction with an aldehyde carrying no alkoxy substituent. In the latter general case, the reaction proceeds rather nonselectively even with the pure Z-enolate of pentan-3-one.[10e] The two enolate approaches to this aldehyde are shown in **13** and **14**, which lead to the 2,3-syn



13



14

and 2,3-anti product, respectively. The selection between the two approaches depends *largely* on the steric bulk of R^2, and thus only enolates with an extremely large R^2 (e.g., *t*-Bu) proceed exclusively through the transition-state **13**.[10b,e] While the size of R^2 is still important in the reaction with **4**, the β-alkoxy substituent in the transition state organizes a rigid framework (with the lithium cation) which would steer the reaction to create the 2,3-syn stereochemistry. More importantly the interaction between the enolate with R^2 and the two groups, methyl and in particular R^1, of the aldehyde causes the energy difference between **6** and **7**, which is translated into the ratio of **8** and **9**. With a small interaction (entries 1–3 in Table II) the ratio ranges between 3.5:1 to 5:1 and increases to approximately 10:1 with R^1 = primary or secondary alkyl and R^2 = secondary alkyl (entries 4, 6, 8). Most significantly, when R^1 carries an additional ethereal substituent, thus creating yet another ligand to coordinate the lithium cation, the observed selectivities (entries 9, 10) now exceed 10:1.[12] The synthetic significance of the above findings will be clearly demonstrated in the following communication.

Acknowledgment. We thank Dr. M. Hirama of these laboratories for his exploratory work in this project and the National Institutes of Health (CA 28337) for financial support. High-resolution mass spectra were provided by the facility supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann), from the Biotechnology Resources Branch, Division of Research Resources.

Registry No. (±)-**4a**, 79027-30-8; (±)-**4b**, 82892-19-1; (±)-**4c**, 82892-20-4; (±)-**4d**, 82892-21-5; (+)-**4e**, 82892-22-6; **5** (R^2 = Et), 74016-27-6; **5** (R^2 = Cy), 82892-23-7; **5a**, 51425-54-8; **5b**, 76436-98-1; (±)-**8** (R = CH_2OCH_2Ph; R^1 = H; R^2 = Et), 82892-24-8; (±)-**8** (R = CH_2OCH_2Ph; R^1 = H; R^2 = Cy), 82892-25-9; (±)-**8** (R = CH_2OCH_2Ph; R^1 = Et; R^2 = Et), 82892-26-0; (±)-**8** (R = CH_2OCH_2Ph; R^1 = Et; R^2 = Cy), 82892-27-1; (±)-**8** (R = CH_2OCH_2Ph; R^1 = CD_2Ph; R^2 = Et), 82892-28-2; (±)-**8** (R = CH_2OCH_2Ph; R^1 = CD_2Ph; R^2 = Cy), 82892-29-3; (±)-**8** (R = CH_2OCH_2Ph; R^1 = *i*-Pr; R^2 = Et), 82892-30-6; (±)-**8** (R = CH_2OCH_2Ph; R^1 = *i*-Pr; R^2 = Cy), 82892-31-7; **8** (R = CH_2OCH_2Ph; R^1 = $CH_2CH_2DSiMe_2Bu$-*t*; R^2 = Et), 82892-32-8; **8** (R = CH_2OCH_2Ph; R^1 = $CH_2CH_2OSiMe_2Bu$-*t*; R^2 = Cy), 82892-33-9; (±)-**9** (R = CH_2OCH_2Ph; R^1 = H; R^2 = Et), 82916-75-4; (±)-**9** (R = CH_2OCH_2Ph; R^1 = H; R^2 = Cy), 82916-76-5; (±)-**9** (R = CH_2OCH_2Ph; R^1 = Et; R^2 = Et), 82916-77-6; (±)-**9** (R = CH_2OCH_2Ph; R^1 = Et; R^2 = Cy), 82916-78-7; (±)-**9** (R = CH_2OCH_2Ph; R^1 = CD_2Ph; R^2 = Et), 82916-79-8; (±)-**9** (R = CH_2OCH_2Ph; R^1 = CD_2Ph; R^2 = Cy), 82916-80-1; (±)-**9** (R = CH_2OCH_2Ph; R^1 = *i*-Pr; R^2 = Et), 82916-81-2; (±)-**9** (R = CH_2OCH_2Ph; R^1 = *i*-Pr; R^2 = Cy), 82916-82-3; **9** (R = CH_2OCH_2Ph; R^1 = $CH_2CH_2OSiMeBu$-*t*; R^2 = Et), 82916-83-4; **9** (R = CH_2OCH_2Ph; R^1 = $CH_2CH_2OSiMeBu$-*t*; R^2 = Cy), 82916-84-5; **10a**, 51425-53-7; **10b**, 76437-07-5; **11a**, 96-22-0; **11b**, 1123-86-0; **12**, 82892-34-0; $(i\text{-Pr})_2NLi$, 4111-54-0; $(Me_3Si)_2NLi$, 4039-32-1; $(Et_3Si)_2NLi$, 82892-35-1; $(PhMe_2Si)_2NH$, 3449-26-1; $(Et_3Si)_2NH$, 2117-18-2.

Supplementary Material Available: Listing of spectral data and comments (6 pages). Ordering information is given on any current masthead page.

(11) Zhinkin, D. Y.; Mal'nova, G. N.; Gorislavskaya, Zh. V. *Zh. Obshch. Khim.* **1968**, *38*, 2800.

(12) It should be cautioned that when the lithium or magnesium enolate is generated from a methyl or ethyl ketone with an R^2 carrying an alkoxy group in **11**, the cation definitely coordinates *intramolecularly* with this ethereal substituent, unless it is protected with a bulky group.[6] In the aldol reaction of such an enolate with **4**, the *intermolecular* coordination of the cation with the alkoxyl substituent of **4** is lessened significantly and is perhaps nearly nonexistent in some cases. The stereochemical outcome of this reaction should be different from that described in the text. Examples are found in the last aldol reaction used to combine two major fragments of monensin. Monensin: (a) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2120. (b) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *Ibid.* **1979**, *101*, 262. Other examples: (c) Masamune, S., to be submitted for publication.

Synthesis of Ansamycins: The Ansa Chain of Rifamycin S

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Received May 20, 1982

The antibiotic rifamycin S (**1**)[1] is a well-known representative member of the ansamycin family.[2] The unique structure of this compound[3] is characterized by the naphthoquinone moiety bridged at the 2- and 12-positions by the "ansa" chain (**2**, Scheme I), which is rich in chirality. Our synthetic interest in this chain arises from the presence of a symmetry element that becomes all the more evident with two retrosynthetic operations: (1) oxidation of the C(23)-hydroxyl group to the ketone and (2) hydration of the C(18)–C(19) double bond (see **3**). The C(18)–C(28) fragment, incorporating all the chiral centers in **3**, now has C_s symmetry (if R^2 = Me). Dissection of **3** leads to a set of four units, A, B, A′, C (retrosynthesis I), or another set, A, B, C, D (retrosynthesis II), the former (I) being more symmetrical than the latter. Note that (1) units A and A′ are enantiomeric and are readily available in >99% optically pure form through a diastereoselective aldol reaction[4] and that (2) each half [C(18)–C(23) and C(23)–C(28)] of the fragment **3** constitutes a 2,3-*syn*,3,4-*anti*,4,5-*syn*-2,4-dihydroxy-3,5-dimethylcarbonyl system (numbering starts with the carbonyl group)[5] whose stereoselective synthesis can now be achieved again by a single aldol reaction.[6] Thus full recognition and *utilization* of this symmetry will simplify, to a great extent,

(1) For the isolation of **1** from the fermentation broths of *Nocardia mediterranei* (formerly known as *Streptomyces mediterranei*), see: Sensi, P.; Greco, A. M.; Ballotta, R. *Antibiot. Ann.* **1960**, 262.

(2) For reviews of the ansamycins: (a) Brufani, M. In "Topics in Antibiotic Chemistry"; Sammes P., Ed.; Ellis Horwood: Sussex, 1977; Vol. 1, Part B. (b) Rinehart, K. L., Jr.; Shield, L. S. In "Progress in the Chemistry of Organic Natural Products"; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1976; Vol. 33, pp 231–307.

(3) For the classical chemical degradation work, see: (a) Prelog, V. *Pure Appl. Chem.* **1963**, *7*, 551. (b) Oppolzer, W.; Prelog, V. *Helv. Chim. Acta* **1973**, *56*, 287. For the crystallographic analysis of rifamycin B *p*-iodoanilide, see: (c) Brufani, M.; Fedeli, W.; Giacomello, G.; Vaciago, A. *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* **1964**, *36*, 113; *Experientia* **1964**, *20*, 339.

(4) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

(5) For the definition of syn and anti, see: Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.*, preceding communication in this issue.

(6) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.*, preceding communication in this issue.

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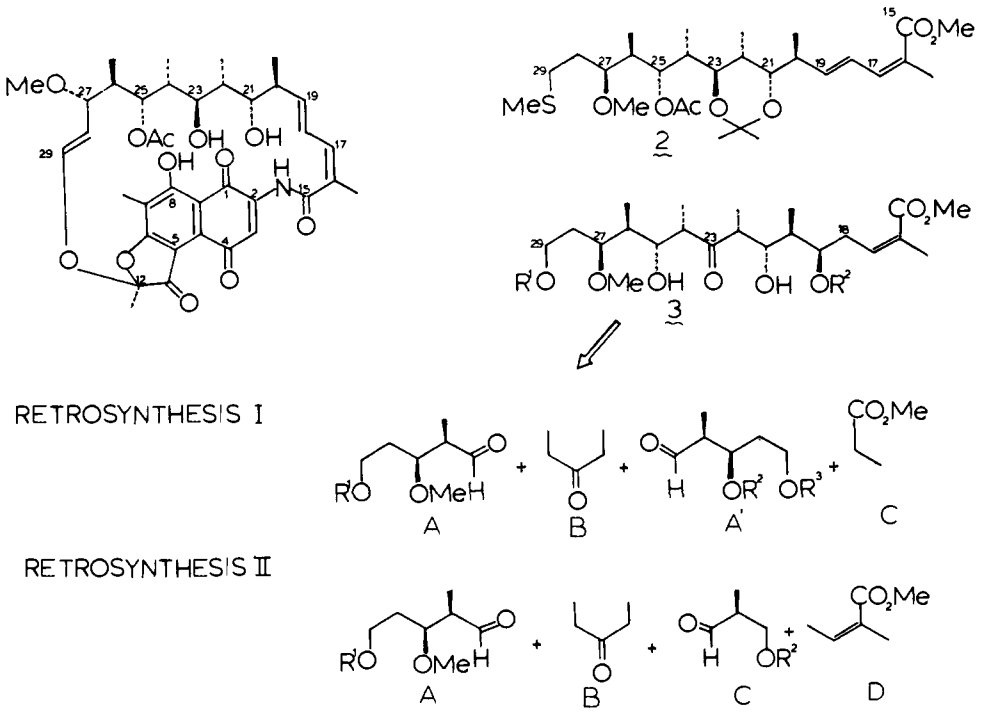
Scheme I



the synthetic scheme leading to **2**, as compared with those (three approaches) recently documented by Kishi and co-workers.[7,8] While these achievements at Harvard are indeed monumental, the above aldol approaches were considered worth pursuing. We outline herein a synthesis of **2** based on retrosynthesis II, which has been adopted first, as this approach offers the advantage of confirming the stereochemistry of a synthetic intermediate halfway in the entire sequence (see below). It is gratifying that even with this less symmetrical design, the 18-step synthesis[9] proceeds in overall 30% yield and with 80% overall stereoselectivity.[7]

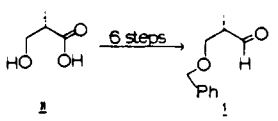
The C(19)–C(29) Fragment (Scheme II). The synthesis starts with the known (−)-3-hydroxy-2-methylcarboxylic acid **4** [which is readily prepared enantioselectively (99% ee) from 3-(benzyloxy)propanal through a boron-mediated aldol reaction followed by a two-step modification of the resulting aldol product[4]]. A sequence of reactions, permethylation (CH_2N_2 with HBF_4),[10] reduction ($LiAlH_4$), and oxidation ($C_5H_5NHCrO_3Cl$, CH_2Cl_2),[11] converts **4** into the aldehyde **5** through **6** and **7** (88% overall yield). The next step concerning the stereoselective construction of the C(24) and C(25) chiral unit utilizes the simple methodology discussed in the preceding communication.[6] Thus, the aldol reaction of **5** with the *Z*-enolate generated from pentan-3-one with lithium 1,1,3,3-tetramethyl-1,3-diphenyldisilazide proceeds smoothly to provide the ethyl ketone **8** in >95% yield and with 20:1 stereoselection. The C(25) hydroxyl group of **8** is protected by a bulky group[12] (*t*-$BuMe_2SiOTf$)[13] and then the enolates of the resulting silylated ketone **9** (see below) are reacted with (*S*)-3-((β-(trimethylsilyl)ethoxy)methoxy)isobutyraldehyde (**10**)[14] (SEM = (β-(trimethylsilyl)ethoxy)methyl) to provide a major aldol product (20,21-*anti*,21,22-*syn*-**11**) accompanied by the corresponding 20,21-syn,21,22-syn stereoisomer. As expected from the structure of **10** having the *primary* SEM–O substituent,[6] the diastereoselectivity of this aldol reaction is only modest, 3:1 and 5:1 ratios with the lithium and magnesium enolates, respectively.[15] However, addition of bis(cyclopentadienyl)zirconium dichloride[16] to the lithium enolate prior to the reaction with **10** enhances the ratio to 8:1 and at the same time ensures the minimal formation of a third 21,22-antiproduct (~5%).[16,17]

The reduction of **11** with diisobutylaluminum hydride in ether at −78 °C proceeds with 16:1 stereoselection to provide **12**,[18a] which

(7) The first synthesis (racemic)[8a,b] involves 51 steps with 0.7% overall yield and 50% overall stereoselectivity; the second,[8f] 48 steps, 3.1% yield (assuming that 5 steps with unspecified yields proceed quantitatively), 74% stereoselectivity; the third,[8f] 45 steps, 4.3% yield with the above assumption, 75% stereoselectivity.

(8) (a) Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163. (b) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. Also see: (c) Iio, H.; Nagaoka, H.; Kishi, Y. *Ibid.* **1980**, *102*, 7965. (d) Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899. (e) Iio, H.; Nagaoka, H.; Kishi, Y. *Ibid.* **1981**, *22*, 2451. (f) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *23*, 3873. For an approach using monosaccharides, see: (g) Nakata, M.; Takao, H.; Ikeyama, Y.; Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1749.

(9) For a fair comparison of the present synthesis with those reported by Kishi and co-workers,[7,8] the number of steps involved in their syntheses is counted from compound i, which was prepared from (*S*)-3-hydroxyisobutyric



acid (ii) via six steps. The carboxylic acid ii is in turn prepared by enzymatic oxidation of isobutyric acid ((a) Goodhue, C. T.; Schaffer, J. R. *Biotechnol. Bioeng.* **1971**, *13*, 203) or by a diastereoselective aldol reaction with formaldehyde followed by a two-step functional group modification ((b) Choy, W.; Ma, P.; Masamune, S. *Tetrahedron Lett.* **1981**, *22*, 3555). For our synthesis, **4** is taken as the starting material.

(10) Neeman, M.; Johnson, W. S. "Organic Synthesis"; Wiley: New York, 1973; Collect. Vol. 5, p 254.

(11) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(12) In order to maximize the *intermolecular* coordination of the cation (used in the aldol reaction) with an ethereal oxygen of a reacting aldehyde, the *intramolecular* coordination must be suppressed with a bulky protecting group. See footnote 12 of ref 6.

(13) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(14) The aldehyde **10** was prepared from ii via four steps: esterification (CH_2N_2), SEM protection [$Me_3Si(CH_2)_2OCH_2Cl$], reduction ($LiAlH_4$), and Collins oxidation. For the use of SEM, see: Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, 3345.

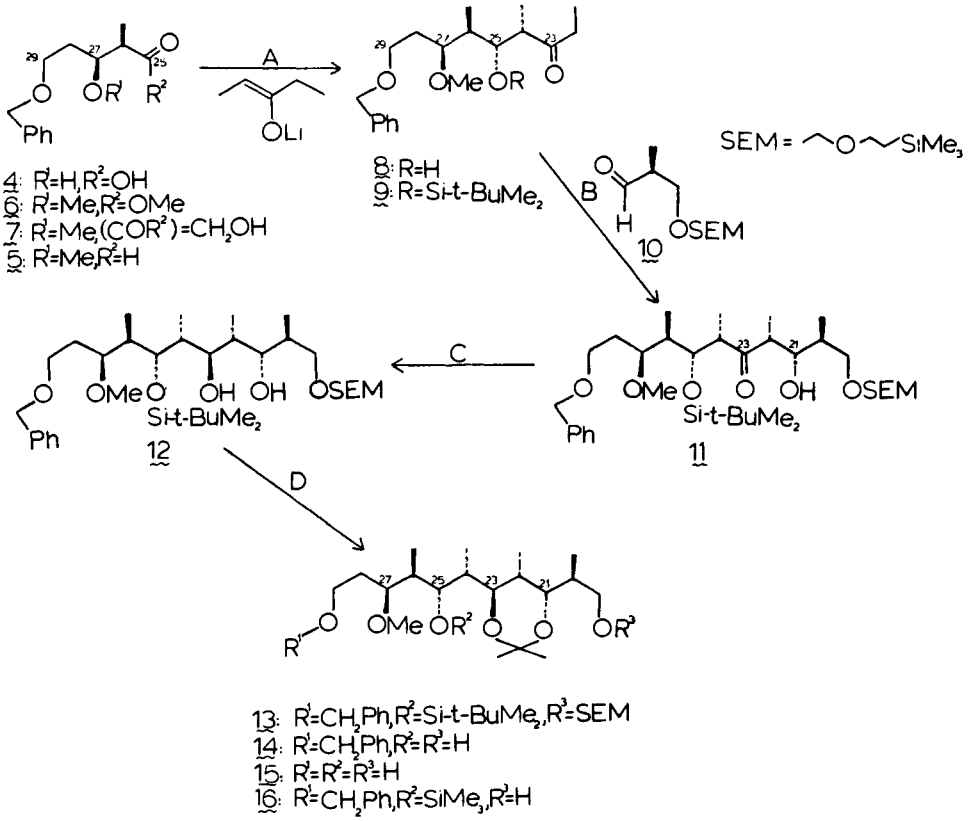
(15) The lithium enolate was generated with lithium 1,1,3,3-tetramethyl-1,3-diphenyldisilazide in THF at −78 °C for 24 h, and anhydrous magnesium bromide was added to this solution for the conversion to the corresponding magnesium enolate.

(16) (a) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, 4607 (b) Evans, D. A.; McGee, L. R. *Ibid.* **1980**, 3975.

(17) A second approach based on retrosynthesis I uses a secondary β-alkoxy aldehyde (A′) (instead of a primary β-alkoxy aldehyde, **10**) in this aldol step. Therefore, in this new approach, which is now under investigation, the stereoselectivity of the reaction is expected to be high.[6]

(18) For comments on this reaction, see the supplementary material. a–c indicate the corresponding sections of this attachment.

Scheme II[a]



[a] Key: (A) 5 → 8, Et_2CO $(PhMe_2Si)_2NH$, *n*-BuLi (THF), −78 °C; 8 → 9, *t*-$BuMe_2SiOTf$, 2,6-lutidine (CH_2Cl_2) 0 °C; (B) $(PhMe_2Si)_2NH$, *n*-BuLi (THF), −78 °C followed by $(C_5H_5)_2ZrCl_2$ −40 → −20 °C; (C) Dibal (Et_2O), −78 °C; (D) **12** → **13**, $Me_2C(OMe)_2$, Me_2CO, concentrated H_2SO_4 (cat.), 0 °C; **13** → **16**, *n*-Bu_4NF, 2 M/THF, 40 °C, 36 h; Me_3SiCl, imidazole (THF).

is then converted into the corresponding acetonide **13**. At this stage the stereochemistry of **13** was correlated with that of a degradation product of rifamycin S. Thus, removal of the silyl protecting groups from **13** (*n*-Bu_4NF) and debenzylation of the resulting diol **14** (H_2, Pd/C) lead to the triol **15**, which has been found to be identical with the corresponding compound derived from the natural product.[18b] Thus, the *seven-step sequence* converts the starting material **4** into **12**, which incorporates *all eight chiral centers* present in the ansa chain.

Silylation of **14** (Me_3SiCl, imidazole) followed by aqueous workup provides the C(25) silyloxy compound **16**, which is ready for the next stage of the ansa chain synthesis. The overall yield from **12** to **16** is 79%.

Ansa Chain (Scheme III). The addition of a five-carbon [C(15)–C(18)] unit to the C(19)–C(29) fragment to construct a (*Z*,*E*)-dienoic acid system is patterned after the methodology originally developed for the synthesis of monomethyl (*Z*,*E*)-muconate by Linstead and co-workers.[19] Thus, Collins–Ratcliffe oxidation of **16** provides the aldehyde **17**, which without purification is reacted with the lithio dianion of benzyl 2-methylacetoacetate[20] to yield the β-keto ester **18** (88%, two steps). The number of diastereoisomers in this and subsequent steps is irrelevant, since all will be converted to a single final product. The chemoselective reduction ($NaBH_4$, MeOH, −30 °C) of the keto functionality in **18**, followed by hydrogenolysis (H_2, Pd/C, 95% EtOH) and finally warming of the resulting trihydroxycarboxylic acid in refluxing toluene, causes complete lactonization of all the stereoisomers (>95%, three steps). Treatment of the trihydroxy-δ-lactone **19** with trifluoroacetic anhydride and triethylamine effects acylation of the C(29) and C(25) hydroxyl groups with the concomitant elimination of the C(17) hydroxyl group. Subsequently the C(29) trifluoroacetate is selectively hydrolyzed and then replaced by the tosyl group to form **20** (85%, three steps). The ensuing step is highly gratifying. Reaction of **20** with excess sodium methanethiolate[18c] in dimethylformamide at room temperature simultaneously brings about three transformations: (1) substitution of the tosylate group; (2) liberation of the C(25) hydroxyl group; (3) the desired lactone ring opening to yield the (*Z*,*E*)-dienoic acid **21** (80%): No other geometrical isomer of this final product is found. Esterification (CH_2N_2) and acetylation completes the synthesis of **2**,[21] which has already been converted to rifamycin S.[8a,c]

In concluding this series, a few brief comments appear to be appropriate. Our aldol chemistry, which began with boron enolate chemistry 3 years ago,[22] has made considerable progress. The initial investigation, which dealt mainly with the control of the 2,3-stereochemistry of aldol products, soon entered into its second generation through the modest but important demonstration of the 3,4-stereochemical control using chiral enolate reagents derived from the enantiomers of atrolactic acid.[23] With the advent of highly diastereoface-selective enolate reagents,[4] as well as a clearer understanding of metal coordination,[6] one can now draw efficient and reasonably short synthetic schemes for most of the macrolide antibiotics of medium complexity as exemplified in this series and in an earlier communication.[24] The aldol methodology certainly offers one distinct advantage: it creates two new chiral centers in one step. While several other problems remain to be solved, the developments described in this series have provided answers

(19) (a) Elvidge, J. A.; Linstead, R. P.; Sims, P.; Orkin, B. A. *J. Chem. Soc.* **1950**, 2235. For utilization of this concept in model studies for the synthesis of **2** see: (b) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 2317.

(20) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

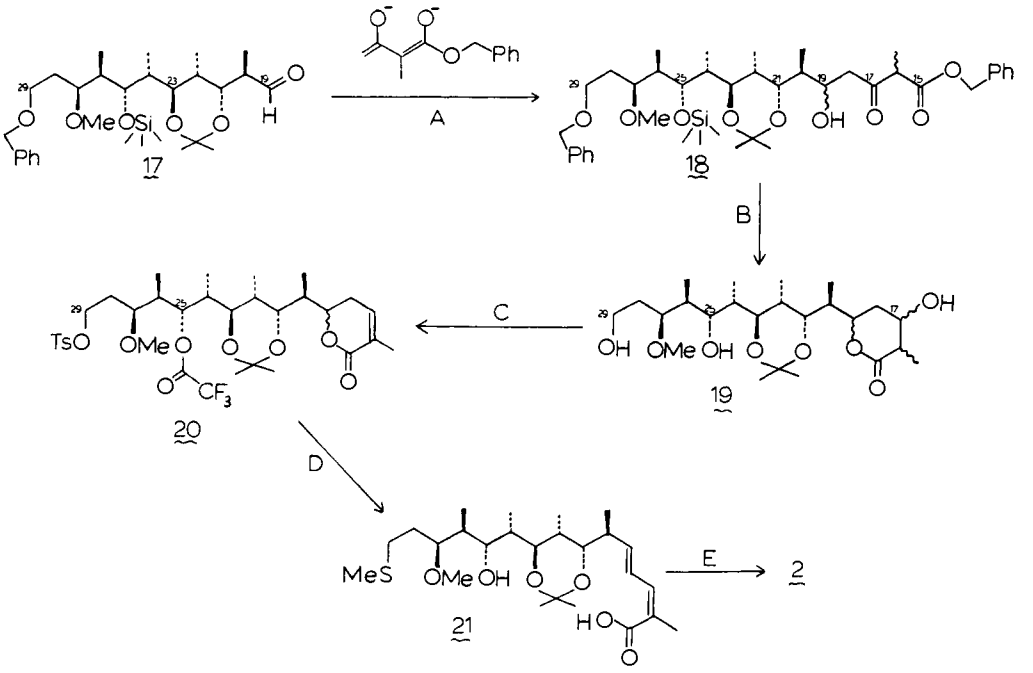
(21) ^1H NMR spectra of our sample (**2**) and Kishi's (supplementary material of ref 8b) were identical. The stereochemistry of the ansa chain is already established at the stage of intermediate **15**.[10b]

(22) Masamune, S.; Mori, S.; Van Horn, D. E.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665.

(23) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

(24) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

Scheme III[a]



[a] Key: (A) $(2\text{-}C_3H_7)_2NH$, *n*-BuLi (THF), −78 °C; (B) $NaBH_4$ (MeOH), −30 °C; 5% Pd–C, H_2(EtOH), 1.5 h, Δ, toluene; (C) $(CF_3CO)_2O$, Et_3N, (C_6H_6); TosCl, C_5H_5N, (CH_2Cl_2), 0 °C, 48 h; (D) MeSNa (excess), (DMF), room temperature, 10 min; (E) CH_2N_2 (Et_2O); Ac_2O, C_5H_5N, 70 °C, 36 h.

for a majority of the questions raised in our earlier review article.[25] Furthermore, the major problems associated with the more general subject of acyclic stereoselection,[26] which concern the diastereofacial selectivity of a chiral reagent or substrate or their interactions, are now clearly recognized.

Acknowledgment. We thank Drs. Sk. Asrof Ali and Tatsuo Toyoda of these laboratories for their important exploratory and degradative[10b] work in this project and Dr. Giancarlo Lancini, Gruppo Lepettit, Milano, for a generous gift of rifamycin S. We also thank the National Institutes of Health (CA 28337) and Hoffmann-La Roche for financial support. B.I. was a recipient of a Kennedy Memorial Trust Fellowship (September 1979–August 1981) and D.S.G. is a National Cancer Institute Trainee (NCI, 2-T32-CA 09112). High-resolution mass spectra were provided by the facility supported by the National Institutes of Health (Grant RR 00317; principal investigator, Professor K. Biemann), from the Biotechnology Resource Branch, Division of Research Resources.

Registry No. 2, 76123-20-1; **4**, 77302-12-6; **5**, 82849-04-5; **6**, 82849-02-3; **7**, 82849-03-4; **8**, 82849-05-6; **9**, 82864-88-8; **10**, 82849-06-7; **11**, 82849-07-8; (20*R*)-**11**, 82890-02-6; **12**, 82849-08-9; **13**, 82849-09-0; **14**, 82849-10-3; **15**, 82849-11-4; **16**, 82849-12-5; **17**, 82849-13-6; **18**, 82849-15-8; **19**, 82849-16-9; **20**, 82849-17-0; **21**, 82849-18-1; iii, 68210-62-8; iv, 82849-24-9; 3-pentanone (ion 1−), lithium, 74016-27-6; benzyl 2-methylacetoacetate lithio dianion, 82849-14-7; methyl 2*S*-methyl-3-[(2-trimethylsilylethoxy)methoxy]propanoate, 82849-19-2; 2*S*-methyl-3-[(2-trimethylsilylethoxy)methoxy]propanol, 82849-20-5; 4*R*-[(2*R*,6-dihydroxy-1*S*,3*R*-dimethyl-4*S*-methoxy)hex-1-yl]-6*R*-[2-[2-(trimethylsilylethoxy)methoxy]-1*S*-methylethyl]-2,2,5*R*-trimethyl-1,3-dioxane, 82849-21-6; 4-[6-benzyloxy-1,3-dimethyl-4-methoxy-2-(trimethylsilyloxy)hex-1-yl]-6-[benzyl 3,5-dihydroxy-2,6-dimethylhexanoate-6-yl]-2,2,5-trimethyl-1,3-dioxane, 82864-89-9; 4*R*-[1*S*,3*R*-dimethyl-6-hydroxy-4*S*-methoxy-2*R*-(trifluoroacetate)hex-1-yl]-6*R*-[1-[3-methyl-5,6-dihydropyran-2-on-6-yl]ethyl]-2,2-5*R*-trimethyl-1,3-dioxane, 82849-22-7; 4*R*-[1*S*,3*R*-dimethyl-2*R*-hydroxy-4-methoxy-6-methylthio]-6*R*-[methyl 2-methylhept-2(*Z*),4(*E*)-dienoate-6*S*-yl]-2,2,5*R*-trimethyl-1,3-dioxane, 82849-23-8; rifamycin S, 13553-79-2.

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Supplementary Material Available: Listing of spectral data and comments (6 pages). Ordering information is given on any current masthead page.

Directed Metalation of Tertiary Benzamides. Ortho *N*-Aryl Amination and Synthesis of Acridones

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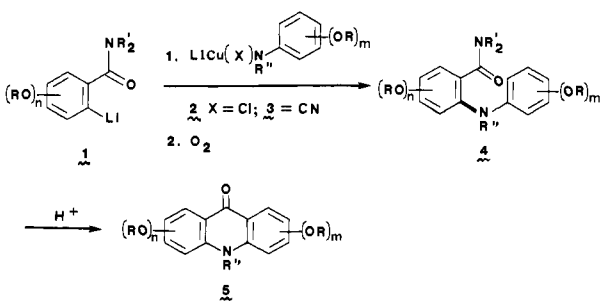
Received July 19, 1982

Umpolung methodology for direct formation of C–N bonds (i.e., $R\text{–}M + R^1R^2N^+ \rightarrow R\text{–}NR^1R^2$; M = metal)[1] is assuming significance as a result of the rapidly increasing accessibility of diverse organometallic reagents. Although numerous formally electrophilic nitrogen species have been investigated,[2] general and efficient utility of such reagents for the introduction of the $^+NH_2$ moiety has only recently surfaced, e.g., $PhSCH_2N_3$,[3] vinyl azides,[4] $H_2NOMe/MeLi$.[5] We report on the oxidative coupling reaction of ortho-lithiated benzamides (**1**) with anilido–chloro (**2**) or –cyano (**3**) cuprates to yield substituted *N*-arylanthranilamides (**4**, eq 1). We further delineate the direct conversion of this class of com-



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