## Synthesis of Rimocidinolide Methyl Ester, the Aglycone of (+)-Rimocidin**

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Polyene macrolide antibiotics have found widespread use as antifungal agents.[1] The family of polyene macrolides incorporating a mycosamine sugar represent the most common and widely used members of the class of natural products, and include amphotericin B, nystatin, candidin, pimaricin, and rimocidin.[2] These stereochemically complex, highly oxygenated structures have attracted the attention of synthetic chemists.[3] Amphotericin B was synthesized by Nicolaou and co-workers,[4] and the aglycone of amphotericin B, amphoteronolide B, was prepared by Masamune and co-workers.[5,6] We have been interested in the synthesis of polyene macrolides, but most of our work has focused on the oxopolyene subclass.[7] We report herein the first synthesis of the rimocidin aglycone, rimocidinolide methyl ester (**2**).

Rimocidin (**1**) is a 28-membered polyene macrolide which was isolated from *Streptomyces rimosus* in 1951.[8] Cope et al.
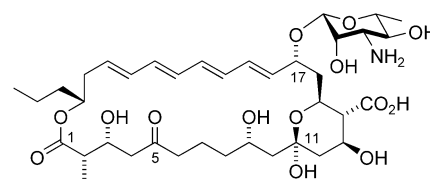
Rimocidin (**1**)

established the carbon skeleton in the mid-1960s,[9] and its flat structure was determined independently by the groups of Borowski and Rinehart in the 1970s.[10] The stereochemistry of rimocidin was determined by Borowski and co-workers group in 1995 through 2D NMR analysis.[11] Rimocidin includes 14 stereogenic centers, a conjugated tetraene, a tetrahydropyran hemiketal, and a macrocyclic lactone and is β-linked to mycosamine. These functionalities make rimocidin sensitive to both strongly acidic and strongly basic reaction conditions. Smith et al. recently reported a synthesis of the C1–C18 segment of rimocidin[12] through a dithiane

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linchpin strategy.[13] Our strategy is based on cyanohydrin acetonide couplings to facilitate the convergent assembly of the rimocidin aglycone.

Cyanohydrin acetonides have been used extensively in our laboratories as synthons for *syn*-1,3-diols,[14] and this strategy has been applied, for example, to syntheses of roxaticin[15] and dermostatin.[16] The structure of rimocidin, however, does not contain any *syn*-1,3-diol segments. In our approach to rimocidin, cyanohydrin acetonides would be used as synthons for β-hydroxyketones rather than for syn-1,3-diol acetonides. Thus the cyanohydrin would revert to its earlier application as an acyl anion equivalent,[17] and the strategy is comparable to the widely used dithiane disconnection.[18]

A retrosynthetic analysis of rimocidinolide methyl ester (**2**) is presented in Scheme 1. The macrolide ring would be
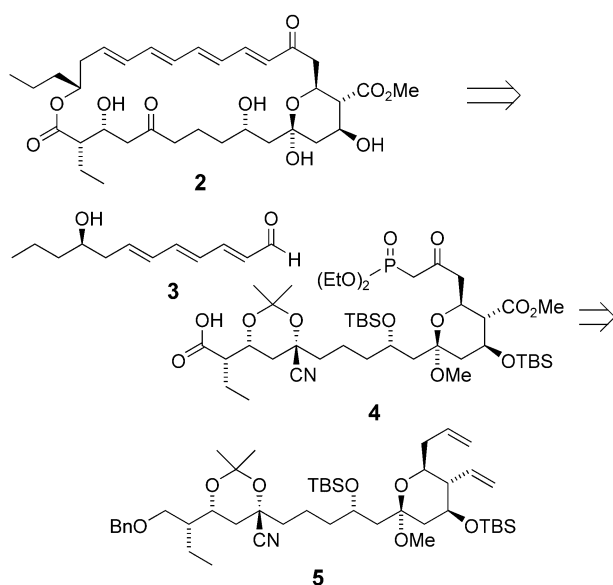
Scheme 1. Retrosynthetic analysis of rimocidinolide methyl ester **2**.

prepared from two segments, an unsaturated aldehyde **3** and the complex phosphonate **4**. Two bonds would be formed between **3** and **4**: an ester linkage and an alkene. The ester and alkene could be formed in either order, but in general the Horner–Emmons cyclization route has better precedent and would be investigated first. The phosphonate **4** would be prepared from protected polyol **5**. We planned to assemble the polyol **5** through cyanohydrin acetonide couplings.

The most complex segment of the polyol chain is the C12–C17 segment **10**, the precursor to the hemiacetal ring. Its synthesis, based on an enantioselective aldol reaction, is outlined in Scheme 2. An Evans aldol reaction[19] between **7** and aldehyde **6** gave the expected product contaminated with the deconjugated crotonate. The aldol adduct was most conveniently isolated after conversion into its Weinreb amide **8**.[20] Treatment with allyl magnesium bromide and subsequent *anti*-selective reduction with the Evans triacetoxyborohydride[21] generated diol **9** as a single diastereomer. Acetonide formation did not proceed to completion, and the recovered starting material was recycled to improve material through-
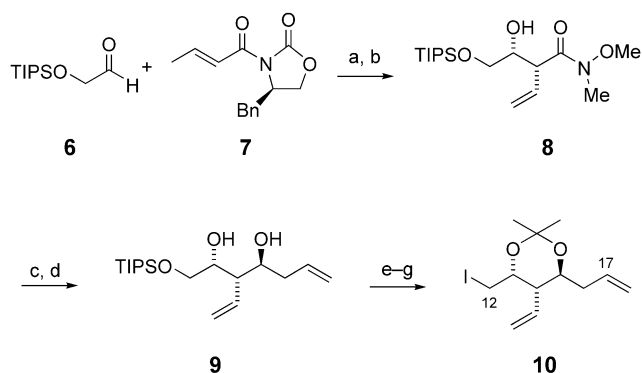
Scheme 2. Reagents and conditions. a) Bu$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, then **6**, −78 °C; b) MeONHMe·HCl, Me$_3$Al, CH$_2$Cl$_2$, 53% over two steps; c) AllylMgBr, THF, −10 °C, 92%; d) Me$_4$N(AcO)$_3$BH, CH$_3$CN/HOAc, −20 °C, 94%; e) 2,2-DMP, acetone, CSA, reflux, repeat; f) TBAF, THF, 99% over two steps; g) I$_2$, PPh$_3$, imidazole, benzene/Et$_2$O, 99%. TIPS = triisopropylsilyl, Tf = trifluoromethanesulfonyl, 2,2-DMP = 2,2-dimethoxypropane, CSA = ±-camphorsulfonic acid, TBAF = tetrabutylammonium fluoride.

put. Cleavage of the TIPS group and introduction of the iodide substituent with PPh$_3$ and I$_2$ completed the synthesis of **10**[22] in an overall yield of 44% in seven steps.

Two cyanohydrin acetonides, **16** and **20**, were prepared for the synthesis. The synthesis of **16** is presented in Scheme 3 and also uses an Evans aldol coupling.[19] Aldol coupling between **11** and aldehyde **12** led to the expected adduct. The optimal procedure for producing diol **13** involved hydrolytic removal of the auxiliary and reduction of the acid with LAH. Direct reduction of the adduct led to complex mixtures. Several approaches were investigated for the selective benzylation of
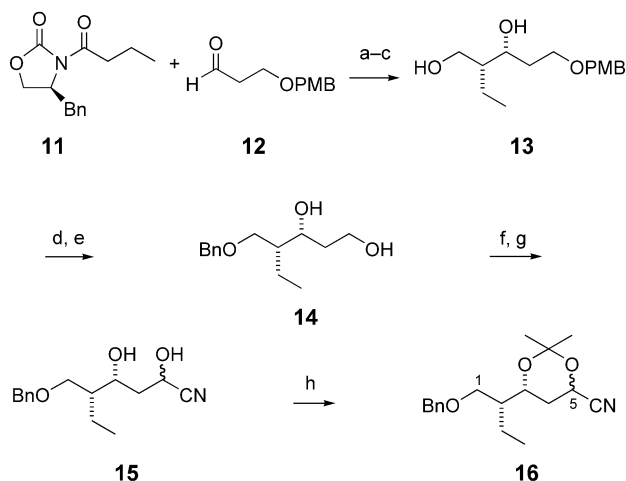

Scheme 3. Reagents and conditions. a) Bu$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, then **12**, −78 °C, 92%; b) LiOH, H$_2$O$_2$; c) LAH, THF, reflux, 74% over two steps; d) NaH, BnBr, DMF, −50 °C, 70%; e) HCl (1 N), EtOH, reflux, 98%; f) TEMPO, KBr, NaOCl; g) TMSCN, KCN·18[crown]-6, 92% over two steps; h) 2,2-DMP, acetone, PPTS, reflux, 97% (3:2 ratio). PMB = *p*-methoxybenzyl, LAH = lithium aluminum hydride, DMF = *N*,*N*-dimethylformamide, TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl, TMS = trimethylsilyl, PPTS = pyridinium toluene-*p*-sulfonate.

the primary alcohol **13**,[23] but the most effective method used excess NaH and 1 equivalent of BnBr.[24] The PMB group was cleaved selectively by treatment with TMSCl, SnCl$_2$, and anisole,[25] but the deprotection step was more conveniently carried out by treatment with HCl (1N) in refluxing ethanol. Conversion of the 1,3-diol into a cyanohydrin acetonide made use of the selective oxidation of primary alcohols to aldehydes with TEMPO.[26] Oxidation of **14** catalyzed by TEMPO led to a solution of the β-hydroxyaldehyde in CH$_2$Cl$_2$. The solution was treated directly with TMSCN and KCN/[18]crown-6 to generate the cyanohydrins **15**. Experience has shown that β-hydroxyaldehydes rapidly dimerize in the absence of solvent, but solutions can be handled without trouble.[27] Acetonide formation catalyzed by PPTS gave the cyanohydrin acetonide **16** as an inconsequential 3:2 mixture of isomers at the cyanohydrin center. We consider this strategy for the conversion of 1,3-diol **14** into cyanohydrin acetonide **16** to be the most reliable and convenient method for the preparation of cyanohydrin acetonides.

Synthesis of the second cyanohydrin is presented in Scheme 4. Enantioselective allylation of aldehyde **17**, followed by ozonolysis and reduction with NaBH$_4$, produced the diol **18** with 89% *ee*. Oxidation with TEMPO, cyanohydrin formation, and acetonide formation completed the five-step synthesis of cyanohydrin acetonide **20**.

The cyanohydrin acetonide segments and iodide **10** were combined as illustrated in Scheme 5. In the past, we alkylated cyanohydrins by forming the anion and then adding the electrophile.[14] Several years ago we reported that deprotonation was compatible with most alkyl halide electrophiles.[28] The alkylation of cyanohydrin **20** was most conveniently and reliably conducted through an in situ deprotonation method. The less precious cyanohydrin **20** was used in twofold excess relative to the iodide **10**.[29] The two segments were combined in THF at −40 °C, and a solution of LDA was added. If the
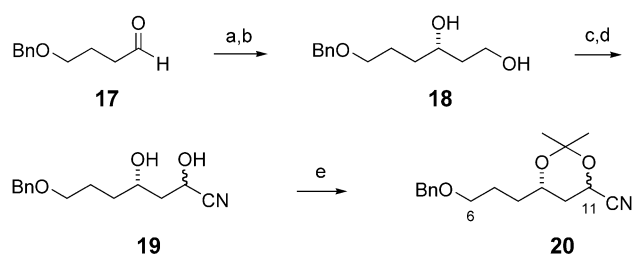

Scheme 4. Reagents and conditions. a) 1. (−)-Ipc$_2$BAllyl, THF, −100 °C; 2. H$_2$O$_2$, NaOH (1 N), MeOH; b) 1. O$_3$, CH$_2$Cl$_2$/MeOH, −78 °C; 2. NaBH$_4$, −78 °C, 82% over two steps; c) TEMPO, KBr, NaOCl; d) TMSCN, KCN·[18]crown-6, 94% over two steps; e) 2,2-DMP, acetone, PPTS, reflux, 88% (1:1 ratio). Ipc = isopinocampheyl.

reaction were incomplete by TLC analysis, more LDA solution was added and the process was repeated until no starting iodide remained. This approach is robust and works well on both small (< 100 mg) and large (ca. 10 g) scales.

The hemiacetal was introduced by deprotection of the cyanohydrin acetonide. Treatment of **21** with acidic Dowex resin in wet methanol liberated the alcohols, and exposure of the solution to Et$_3$N led to spontaneous generation of the hemiacetal **23**. Reprotection of **23** began with methyl acetal formation and protection of the secondary alcohols as TBS ethers. Reductive debenzylation and iodide formation gave iodide **24**. Cyanohydrin **16** (2 equiv) was combined with iodide **24** by using the in situ deprotonation method to yield the alkylated product **5**. Both cyanohydrins **5** and **21** were formed as single isomers in the alkylation steps, apparently owing to a kinetic anomeric effect.[14] Thus the C1–C17 protected polyol segment **5** was prepared in seven steps and in 55% overall yield from iodide **10**.

Oxidation of the diene **5** to a dialdehyde was much more difficult than we had anticipated, and we opted for a selective
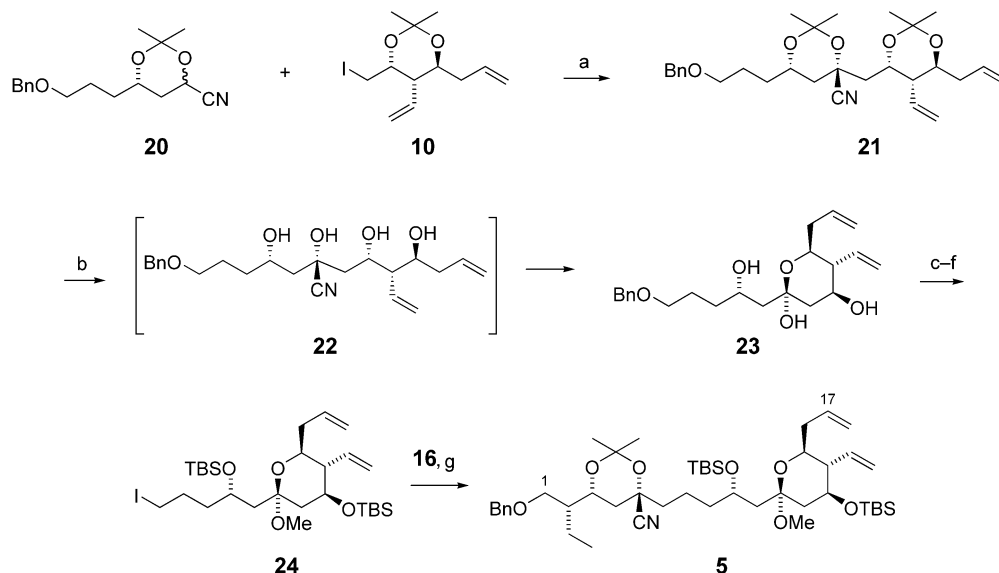
Scheme 5. Reagents and conditions. a) LDA, THF, DMPU, −40 °C, 92%; b) 1. wet MeOH, Dowex 50X2–100; 2. Et$_3$N, 87%; c) HC(OMe)$_3$, MeOH, PPTS, 89%; d) TBSCl, imidazole, DMAP, DMF, 97%; e) Li/NH$_3$, THF, −78 °C, 93%; f) I$_2$, PPh$_3$, imidazole, benzene, 92%; g) LDA, THF, DMPU, −40 °C, 93%. LDA = lithium diisopropylamide, DMPU = N,N′-dimethyl-N,N′-propyleneurea, TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylaminopyridine.
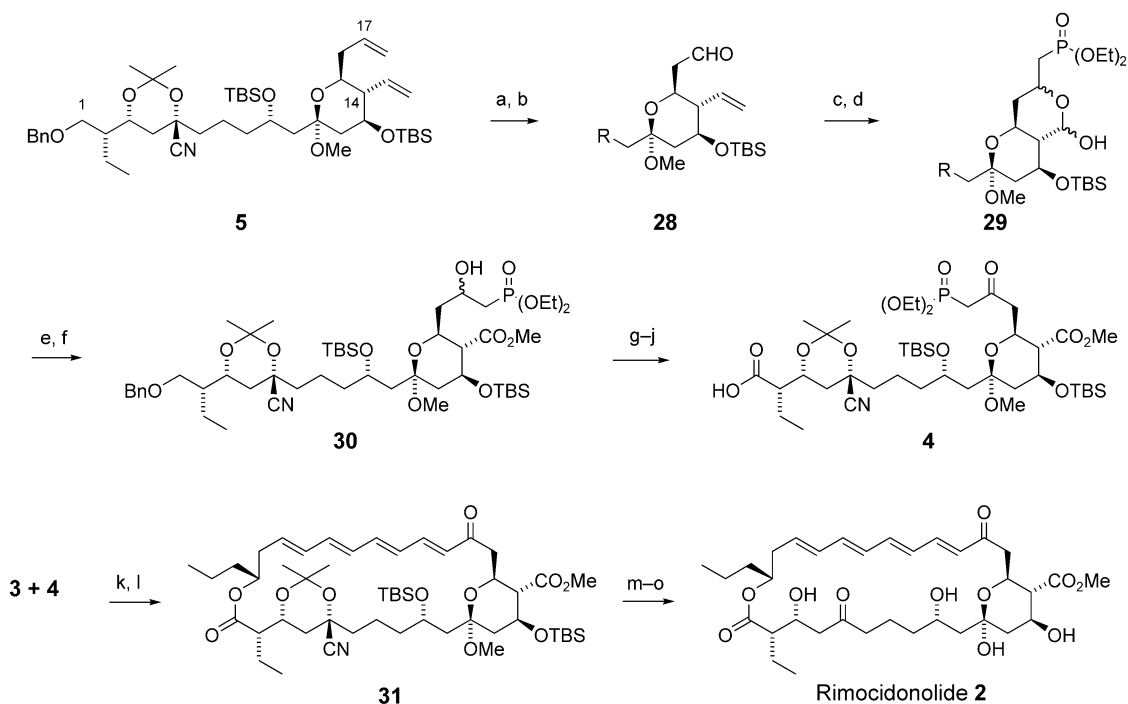
Scheme 6. Reagents and conditions. a) OsO$_4$, NMO, 90%; b) Pb(OAc)$_4$, 91%; c) (EtO)$_2$P(O)CH$_3$, BuLi, THF; d) O$_3$, MeOH/CH$_2$Cl$_2$, −78°C, 95%; e) TPAP, NMO, 87%; f) LiOMe, MeOH, 98%; g) Dess–Martin periodinane, CH$_2$Cl$_2$, 95%; h) Pd(OH)$_2$, H$_2$, EtOAc, 96%; i) Dess–Martin periodinane, CH$_2$Cl$_2$; j) NaClO$_2$, 2-methyl-2-butene, tBuOH, 99% over two steps; k) Yamaguchi esterification, 79%; l) K$_2$CO$_3$, [18]crown-6, toluene, 60°C, 5 h, 74%; m) HF/pyridine, pyridine, THF, 23°C, 30 min; n) HCl (6 N), THF/H$_2$O, 23°C, 5 h; o) Et$_3$N, CH$_2$Cl$_2$, 23°C, 10 min, 55% over three steps. NMO = N-methylmorpholine-N-oxide, TPAP = tetra-n-propylammonium perruthenate.

oxidation route. Osmium tetraoxide selectively oxidized the C17 alkene in preference to the C14 alkene (Scheme 6). Presumably the C14 alkene is hindered by the flanking equatorial substituents. Cleavage of the diol gave the C17 aldehyde **28**, and the phosphonate was introduced by using lithiated diethyl methylphosphonate. Lactol **29** was produced upon ozonolysis. The lactol was converted into the methyl ester by oxidation with TPAP–NMO[30] followed by treatment with lithium methoxide in methanol. Synthesis of phosphonate **4** was completed by oxidation of the alcohol, hydrogenation to cleave the benzyl ether, and then a two-step oxidation of the alcohol function at C1 to an acid. The described conversion of polyol **5** into phosphonate **4** is the result of many different attempts using a variety of approaches. Functional-group interactions thwarted most of the routes investigated. The final route is reliable and avoids the common pitfalls.

The synthesis of rimocidinolide **2** was completed as illustrated in Scheme 6. The acid **4** was esterified with alcohol **3**[31] by using the Yamaguchi protocol.[32] (Alternatives such as DCC, HATU, and PyBOP produced the ester but in lower yields.[33]) An attempted cyclization of the resulting ester with LiCl/DBU resulted in elimination of acid **4**, which was reisolated in 75% yield.[34] On the other hand, Horner–Wadsworth–Emmons macrocyclization with K$_2$CO$_3$ and 18[crown]-6 in toluene produced the macrolide **31** in 74% yield.[35] Deprotection of macrolide **31** began with removal of the TBS ethers with HF–pyridine in pyridine/THF. The methyl acetal was partially removed under these conditions.

Cleavage of the acetonide and hydrolysis of the methyl acetal took place upon treatment with HCl (6 N) in THF. Finally, the C7 ketone was unmasked by brief exposure to Et$_3$N. Thus, rimocidinolide methyl ester (**2**) was synthesized in 29 steps in the longest linear sequence and in 4.3% overall yield from aldehyde **6**. In practice, a number of these steps were combined for convenience. The synthetic rimocidinolide **2** was characterized by NMR and IR spectroscopy as well as HRMS and CD.[36]

The synthesis of the rimocidinolide and in particular of the polyol segment **5** illustrates the usefulness of cyanohydrin acetonides as β-hydroxyketone synthons for the convergent synthesis of polyol chains.[14] Segment **5** was assembled in a 14-step linear sequence in nearly 25% overall yield from aldehyde **6**. The cyanohydrin acetonides **16** and **20** were prepared in high yield from terminal 1,3-diols by using a new protocol. Alkylation of these synthons with alkyl iodides **24** and **10** proceeded in 93% and 92% yields, respectively, through an in situ deprotonation technique. Ketones can be liberated from cyanohydrin acetonides by standard deprotection methods. Cyanohydrin acetonide alkylations represent a very efficient strategy for assembling ketone-containing chains, and this approach complements our previous use of these materials and syn-1,3-diol synthons. Polyol syntheses based on cyanohydrin acetonide couplings are therefore a competitive alternative to the more common dithiane strategies.[18]

[1] S. B. Zotchev, *Current Med. Chem.* **2003**, *10*, 211–223.

[2] S. Omura, H. Tanaka in *Macrolide Antibiotics: Chemistry, Biology, and Practice* (Ed.: S. Omura), Academic Press, New York, **1984**, pp. 351–404.

[3] a) T. Nakata in *Macrolide Antibiotics: Chemistry, Biology, and Practice, 2nd ed.* (Ed.: S. Omura), Academic Press, San Diego, CA, **2002**, pp. 181–284; b) C. Schneider, *Angew. Chem.* **1998**, *110*, 1449–1451; *Angew. Chem. Int. Ed.* **1998**, *37*, 1375–1378; c) J. M. Beau in *Recent Progress in the Chemical Synthesis of Antibiotics* (Eds.: G. Lukacs, M. Ohno), Springer, Berlin **1990**, pp. 135–182.

[4] a) K. C. Nicolaou, R. A. Daines, W. S. Uenishi, W. S. Li, D. P. Papahatjis, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, *110*, 4672–4685; b) K. C. Nicolaou, R. A. Daines, W. S. Uenishi, W. S. Li, D. P. Papahatjis, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, *110*, 4685–4696; c) K. C. Nicolaou, R. A. Daines, Y. Ogawa, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, *110*, 4696–4705.

[5] a) R. M. Kennedy, A. Abiko, T. Takemasa, H. Okumoto, S. Masamune, *Tetrahedron Lett.* **1988**, *29*, 451–454; b) S. Masamune, *Ann. N. Y. Acad. Sci.* **1988**, *544*, 168–179.

[6] For a synthesis of pimaronolide, see: A. J. Duplantier, S. Masamune, *J. Am. Chem. Soc.* **1990**, *112*, 7079–7081.

[7] S. D. Rychnovsky, *Chem. Rev.* **1995**, *95*, 2021–2040.

[8] J. W. Davisson, F. W. Tanner, A. C. Finlay, I. A. Solomons, *Antibiot. Chemother.* **1951**, *1*, 289–290.

[9] A. C. Cope, E. P. Burrows, M. E. Derieg, S. Moon, W. D. Wirth, *J. Am. Chem. Soc.* **1965**, *87*, 5452–5460.

[10] a) L. Falkowski, J. Golik, J. Zielinski, E. Borowski, *J. Antibiot.* **1976**, *29*, 197–198; b) R. C. Pandey, K. L. J. Rinehart, *J. Antibiot.* **1977**, *30*, 146–157.

[11] P. Sowinski, J. Pawlak, E. Borowski, P. Gariboldi, *J. Antibiot.* **1995**, *48*, 1288–1291.

[12] A. B. Smith III, S. M. Pitram, M. J. Fuertes, *Org. Lett.* **2003**, *5*, 2751–2754.

[13] a) A. B. Smith III, A. M. Boldi, *J. Am. Chem. Soc.* **1997**, *119*, 6925–6926; b) A. B. Smith III, S. M. Pitram, A. M. Boldi, M. J. Gaunt, C. Sfouggatakis, W. H. Moser, *J. Am. Chem. Soc.* **2003**, *125*, 14435–14445.

[14] C. J. Sinz, S. D. Rychnovsky, *Top. Curr. Chem.* **2001**, *216*, 51–92.

[15] S. D. Rychnovsky, R. C. Hoye, *J. Am. Chem. Soc.* **1994**, *116*, 1753–1765.

[16] C. J. Sinz, S. D. Rychnovsky, *Angew. Chem.* **2001**, *113*, 3324–3327; *Angew. Chem. Int. Ed.* **2001**, *40*, 3224–3227.

[17] a) G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **1971**, *93*, 5286–5287; b) J. D. Albright, *Tetrahedron* **1983**, *39*, 3207–3233.

[18] M. Yus, C. Najera, F. Foubelo, *Tetrahedron* **2003**, *59*, 6147–6212.

[19] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

[20] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

[21] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

[22] B. Classon, Z. Liu, B. Samuelsson, *J. Org. Chem.* **1988**, *53*, 6126–6130.

[23] a) M. Carmen Cruzado, M. Martin-Lomas, *Carbohydr. Res.* **1988**, *175*, 193–199; b) D. A. Leigh, R. P. Martin, J. P. Smart, A. M. Truscello, *J. Chem. Soc. Chem. Commun.* **1994**, 1373–1374; c) D. L. Boger, J. A. McKie, T. Nishi, T. Ogiku, *J. Am. Chem. Soc.* **1996**, *118*, 2301–2302; d) K. C. Nicolaou, F. L. van Delft, S. R. Conley, H. J. Mitchell, Z. Jin, R. M. Rodriguez, *J. Am. Chem. Soc.* **1997**, *119*, 9057–9058.

[24] A. Fukuzawa, H. Sato, T. Masamune, *Tetrahedron Lett.* **1987**, *28*, 4303–4306.

[25] T. Akiyama, H. Shima, S. Ozaki, *Synlett* **1992**, 415–416.

[26] P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559–2562.

[27] S. D. Rychnovsky, D. J. Skalitzky, *J. Org. Chem.* **1992**, *57*, 4336–4339.

[28] S. D. Rychnovsky, S. S. Swenson, *J. Org. Chem.* **1997**, *62*, 1333–1340.

[29] When the ratio of nitrile **20** to iodide **10** was reduced to 1.5:1, the product **21** was isolated in 85% yield. In practice, the relative value of the nitrile and iodide dictated a higher ratio of the two reagents.

[30] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666.

[31] The synthesis of aldehyde **3** is included in the Supporting Information.

[32] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[33] DCC = 1,3-dicyclohexylcarbodiimide; HATU = *O*-(7-azabenzo-triazol-1-yl)-*N*,*N*′,*N*″,*N*‴-tetramethyluronium; PyBOP = 1-ben-zotriazolyloxy-tris(pyrrolidino)phosphonium.

[34] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

[35] a) G. Stork, E. Nakamura, *J. Org. Chem.* **1979**, *44*, 4010–4011; b) K. C. Nicolaou, S. P. Seitz, M. R. Pavia, N. A. Petasis, *J. Org. Chem.* **1979**, *44*, 4011–4013.

[36] The complete assignment of the ^{1}H NMR spectrum of rimoci-dinolide **2** is listed in the Supporting Information.