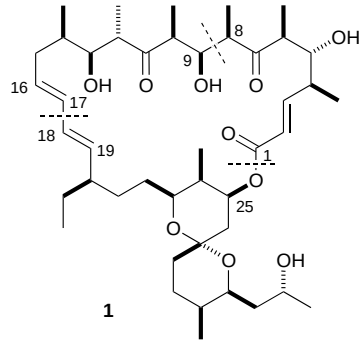
Total synthesis of rutamycin B *via* Suzuki macrocyclization

James D. White,* Thomas Tiller, Yoshihiro Ohba, Warren J. Porter, Randy W. Jackson, Shan Wang, and Roger Hanselmann

Department of Chemistry, Oregon State University, Corvallis, OR 97331-4003, USA

The macrolide rutamycin B containing 17 stereogenic centres and a 26-membered ring was synthesized by a route which features a chelate-controlled, double differentiating aldol reaction and ring closure by means of a vinyl–vinyl coupling.

Rutamycins A and B are structurally complex macrolide antibiotics isolated from *Streptomyces* species.[1] A total synthesis of rutamycin B (**1**) by Evans[2] confirmed the structural assignment,[3] and the absolute configuration of **1** was deduced from synthesis of the spiroketal segment obtained by degradation of the rutamycins.[4] Herein, we report a convergent synthesis of rutamycin B in which the 26-membered ring is closed by means of a Suzuki macrocyclization.

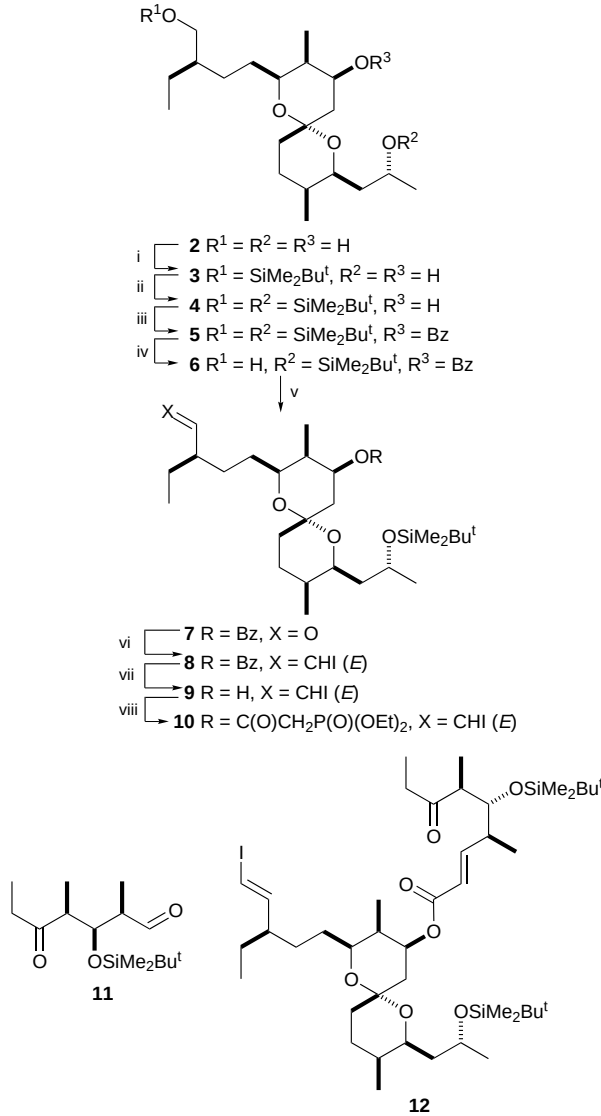


1

Selective silylation of triol **2**[5] took advantage of the different steric environments of the three hydroxy groups in this structure and was accomplished by reaction with Bu^tMe_2SiCl, which gave **3**, and then by treatment with $Bu^tMe_2SiOSO_2CF_3$ to yield **4** (Scheme 1). The remaining secondary alcohol was converted to its benzoate **5**, and the primary silyl ether was selectively removed by treatment with HF·pyridine complex. The resultant primary alcohol **6** was oxidized to aldehyde **7**, which was subjected to a Takai reaction[6] with CHI_3 in the presence of $CrCl_2$ to yield *trans* iodo alkene **8**. After saponification of the benzoate, the liberated alcohol **9** was reacted with diethoxyphosphorylacetyl chloride to give **10**. Horner–Emmons condensation of the lithio anion of **10** with keto aldehyde **11**, previously prepared from methyl (2*R*)-3-hydroxy-2-methylpropionate,[7] afforded α,β-unsaturated ester **12**.

Synthesis of the C9–C16 segment **26** of **1** was initiated by asymmetric crotylation of (*R*)-**13** with (*E*)-crotylboronate **14** derived from (*S*,*S*)-tartrate (Scheme 2).[8] The alcohol **15** resulting from *re* face addition to the aldehyde was converted to the bis(silyl ether) **16**, and the primary ether was selectively cleaved to give **17**. The tosylate **18** of this alcohol was displaced with cyanide and the resultant nitrile **19** was reduced to **20** and then to alcohol **21**. The latter was converted to its bis(silyl ether) **22** before ozonolysis to **23**. The reaction of **23** with (*E*)-crotylboronate **24** derived from (*R*,*R*)-tartrate[8] afforded alcohol **25** with good stereoselectivity (> 95 : 5) in this matched (Felkin) addition to the *si* face of the aldehyde. Alcohol **25** was protected as its *p*-methoxybenzyl (PMB) ether **26** and the latter upon ozonolysis yielded **27**.

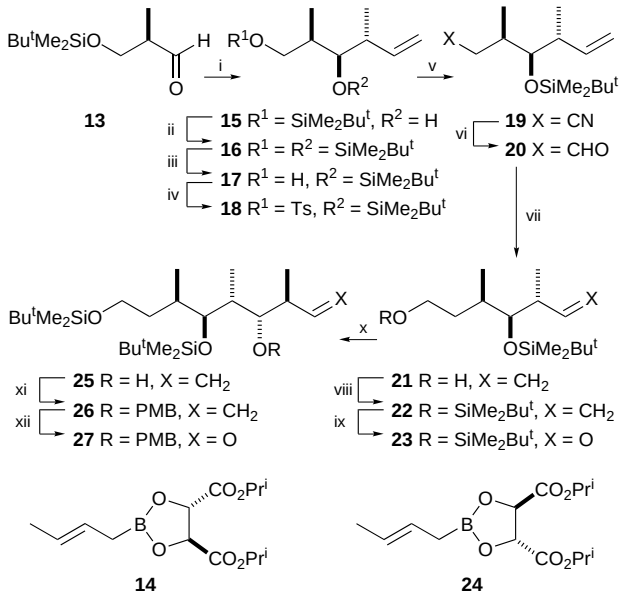
Coupling of the (*Z*)-chlorotitanium enolate[9] of **12** and **17** gave the *syn*,*syn* (Felkin) aldol product **28** as the sole stereoisomer (Scheme 3).[10] A rationale for this high stereoselectivity invoking secondary complexation of the aldehyde carbonyl with the PMB ether has been suggested previously,[7] and it is noteworthy that the aldol reaction of **12** with **27** is completely nonstereoselective when the PMB group of **12** is replaced by a Et_3Si ether. Thus, it appears that the PMB ether not only obstructs the anti-Felkin pathway in this coupling, but



11

12

Scheme 1 *Reagents and conditions*: i, Bu^tMe_2SiCl, pyridine, $AgNO_3$, THF; ii, $Bu^tMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, −78 °C, 66%; iii, BzCl, Et_3N, DMAP, CH_2Cl_2, 90%; iv, HF·pyridine, pyridine, 61%; v, $(COCl)_2$, DMSO, Et_3N; CH_2Cl_2, −78 °C, 96%; vi, CHI_3, $CrCl_2$, THF, 0 °C, 76%; vii, LiOH, MeOH–H_2O–THF, ~100%; viii, $(EtO)_2(O)PCH_2COCl$, pyridine, DMAP, 82%; ix, LDA, THF, then **11**, −78 → 0 °C, 88%

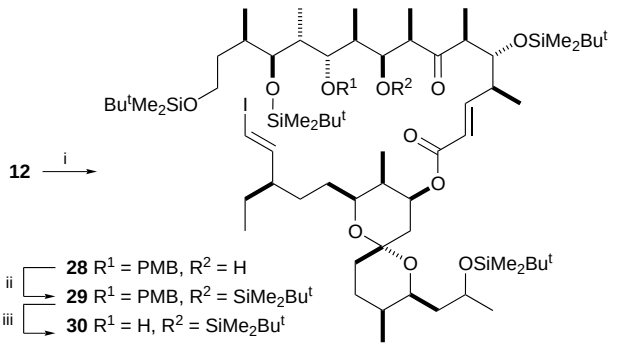


Scheme 2 *Reagents and conditions*: i, **14**, 4 Å MS (powder), toluene, −78 °C, 86% (78% de); ii, $Bu^tMe_2SiOSO_2CF_3$, Et_3N, CH_2Cl_2, 99%; iii, NH_4F, MeOH, heat, 85%; iv, TsCl, pyridine, 92%; v, NaCN, DMSO, 94%; vi, DIBAL-H, toluene, −78 °C, 75%; vii, $NaBH_4$, Pr^iOH, 0 °C, 87%; viii, Bu^tMe_2SiCl, imidazole, DMF, 96%; ix, O_3, CH_2Cl_2–MeOH, −78 °C, Me_2S, 94%; x, **24**, 4 Å MS (powder), toluene, −78 °C, 78% (> 98% de); xi, $PMBOC(=NH)CCl_3$, CF_3SO_3H, −10 °C, 68%; xii, O_3, MeOH–CH_2Cl_2, 79%

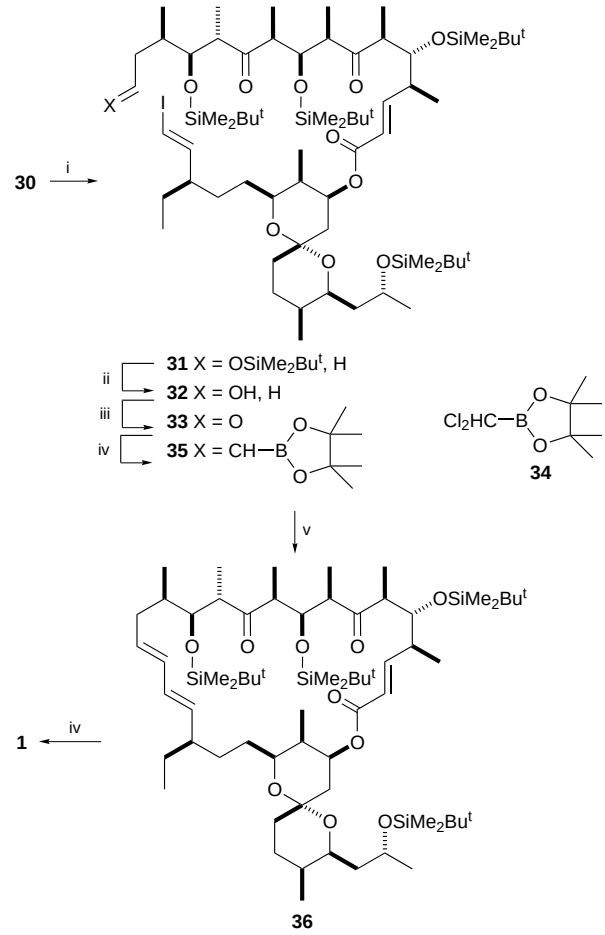
plays a positive role by favouring attack at the *re* face of the aldehyde carbonyl by the *si* face of the titanium enolate.

β-Hydroxy ketone **28** was converted to its silyl ether **29**, and the PMB ether was cleaved to give **30**, which was immediately oxidized to **31** (Scheme 4). The primary silyl ether was selectively removed from **31** and the resultant alcohol **32** was oxidized to **33**. Condensation of **33** with the dichloromethylboronic ester **34**[11] of pinacol in the presence of $CrCl_2$ and LiI afforded (*E*)-vinyl boronate **35**[12] which was subjected to palladium-catalysed intramolecular coupling[13] in the presence of Ag_2O[14] and $AsPh_3$. The ensuing macrocyclization proceeded in good yield and furnished the tetrasilyl ether **36** of rutamycin B, identical in all respects with a sample prepared from the natural material by exhaustive silylation with Bu^tMe_2SiO-SO_2CF_3. Final cleavage of the four Bu^tMe_2Si ethers from **36** by sequential addition of aq. HF in pyridine gave **1**, identical with natural rutamycin B.

We thank Dr Herbert Kirst and Ms Margaret Niedenthal, Eli Lilly Co., Indianapolis (USA) for a sample of natural rutamycin B, and Professor David Evans (Harvard University) for a generous quantity of a derivative of **2**. This research was supported by grants from the U.S. National Institutes of Health (GM50574 and AI10964). Postdoctoral fellowships are gratefully acknowledged by T. T. (Fonds der Chemischen Industrie, Germany) and R. W. J. (US NIH GM16472).



Scheme 3 *Reagents and conditions*: i, $TiCl_4$, Pr^i_2NEt, CH_2Cl_2, −78 °C, then **27**, 52% (> 98% de); ii, $Bu^tMe_2SiOSO_2CF_3$, Et_3N, CH_2Cl_2, 0 °C, 86%; iii, DDQ, H_2O–CH_2Cl_2



Scheme 4 *Reagents and conditions*: i, Dess–Martin periodinane, 93% from **29**; ii, HF·pyridine, MeCN–H_2O–$CHCl_3$, 79%; iii, Dess–Martin periodinane, 95%; iv, **34**, $CrCl_2$, LiI, THF, 76%; v, $Pd(MeCN)_2Cl_2$, $AsPh_3$, Ag_2O, THF, 70%; vi, aq. HF, pyridine, 4 d, 70%

Footnote and References

* E-mail: whitej@ccmail.orst.edu

1 S. Omura, in *Macrolide Antibiotics: Chemistry, Biology, and Practise*, ed. S. Omura, Academic Press, Orlando, Florida, 1984, p. 511.
2 D. A. Evans, H. P. Ng and D. L. Rieger, *J. Am. Chem. Soc.*, 1993, **115**, 11 446.
3 D. Wulthier, W. Keller-Schierlein and B. Wahl, *Helv. Chim. Acta*, 1984, **67**, 1208.
4 D. A. Evans, D. L. Rieger, T. K. Jones and S. W. Kaldor, *J. Org. Chem.*, 1990, **55**, 6260.
5 J. D. White, Y. Ohba, W. J. Porter and S. Wang, *Tetrahedron Lett.*, 1997, **38**, 3167.
6 K. Takai, K. Nitta and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408.
7 J. D. White, W. J. Porter and T. Tiller, *Synlett*, 1993, 535.
8 W. R. Roush, A. D. Palkowitz and K. Ando, *J. Am. Chem. Soc.*, 1990, **112**, 6348.
9 D. A. Evans, D. L. Rieger, M. T. Bilodeau and F. Urpi, *J. Am. Chem. Soc.*, 1991, **113**, 1047.
10 For a similar result in a closely related aldol reaction, see D. A. Evans and H. P. Ng, *Tetrahedron Lett.*, 1993, **34**, 2229.
11 P. M. G. Wuts and P. A. Thompson, *J. Organomet. Chem.*, 1982, **234**, 137.
12 K. Takai, N. Shinomiya, H. Kaihara, N. Yoshida and T. Moriwake, *Synlett*, 1995, 963.
13 A. Suzuki, *Pure Appl. Chem.*, 1994, **66**, 213.
14 T. Gillmann and T. Weeber, *Synlett*, 1994, 649.

Received in Cambridge, UK, 7th October 1997; 7/07251A