

Total Synthesis of Rapamycin**

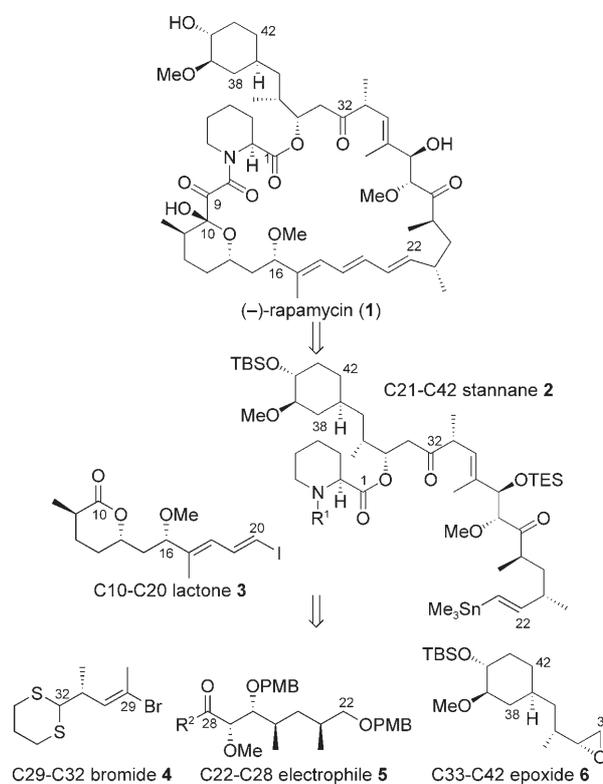
Matthew L. Maddess, Miles N. Tackett, Hidenori Watanabe, Paul E. Brennan, Christopher D. Spilling, James S. Scott, David P. Osborn, and Steven V. Ley*

Rapamycin (**1**) is a macrocyclic natural product first isolated in 1975 from *Streptomyces hygroscopicus* from a soil sample collected on Easter Island (Rapa Nui).^[1,2] While its initial biological activity as an antifungal agent^[3] attracted little attention, it soon became recognized as a potent immunosuppressive agent, which was launched commercially by Wyeth in 1999 for clinical usage following organ transplantation.^[4] Not surprisingly, the interesting architecture and important biological profile of rapamycin (**1**) attracted interest from the organic synthesis community and cumulated in four total syntheses in the 1990s.^[5,6] Several molecules related to rapamycin, such as FK506,^[7] L-685-818,^[8] meridamycin,^[9] ascomycin,^[10] and the antascomicins,^[11] have also been characterized and extensively studied. Over the years, the detailed biology and the molecular targets for these fascinating compounds have gradually been revealed. Despite the importance and obvious value of the immunomodulating effects,^[12] more extensive studies are delineating whole new fundamental signaling pathways that have significant biological ramifications, especially for cancer chemotherapy. Indeed, new analogues of rapamycin, such as CCI-779, RAD001, and AP23573, have been developed and are rapidly progressing through clinical trials for applications as anti-tumor agents.^[13,14]

The mammalian target for rapamycin, mTOR (also known as FRAP, RAFT, RAPT, or SEP),^[15] is a serine/threonine protein kinase, which is involved in a variety of intracellular events and plays a central role in regulating cell proliferation, growth, differentiation, migration, and survival. It is now recognized that deregulation of mTOR signaling occurs in a diverse set of human tumors and confers higher susceptibility to inhibitors of mTOR.^[14] As a consequence, there is renewed chemical interest in the area and, herein, we report a new route for the total synthesis of rapamycin (**1**).

Retrosynthetically, we sought to address the formation of the rapamycin macrocycle by employing a transannular catechol-templated Dieckmann-like reaction that was used with success in our recent synthesis of the related molecule antascomycin B.^[11a] Further disconnection at the central olefin (C20–C21) of the triene through a Pd⁰-catalyzed Stille coupling affords the simplified C10–C20 lactone **3** and C21–C42 vinyl stannane **2**. For the latter stannane (**2**), we envisioned sequential carbanionic coupling of **4**, **5**, and **6**, whose syntheses were designed to highlight chemistry developed by our group (Scheme 1).

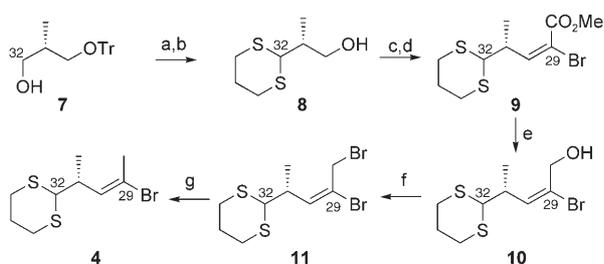
The synthesis of the C29–C32 vinyl bromide **4** commences from the known monoprotected alcohol **7** (Scheme 2).^[16] Swern oxidation followed by dithiane formation with concomitant loss of the trityl group produced **8** in excellent yield. Installation of the correct oxidation state in a protected form at C32 prior to construction of the associated π system at C29–C30 avoided any potential problems of epimerization at the intervening C31 methyl stereocenter later in the synthesis. The requisite olefin geometry was then installed through



Scheme 1. Retrosynthetic analysis for rapamycin (**1**). TBS = *tert*-butyldimethylsilyl; PMB = *para*-methoxybenzyl; TES = triethylsilyl.

[*] Dr. M. L. Maddess, M. N. Tackett, Prof. H. Watanabe, Dr. P. E. Brennan, Dr. C. D. Spilling, Dr. J. S. Scott, D. P. Osborn, Prof. S. V. Ley
Department of Chemistry, University of Cambridge
Lensfield Road, Cambridge CB21EW (UK)
Fax: (+44) 1223-336-442
E-mail: svl1000@cam.ac.uk

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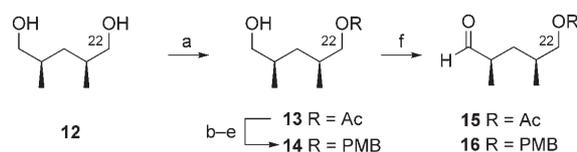


Scheme 2. Reagents and conditions: a) $(\text{COCl})_2$, DMSO, DIPEA, CH_2Cl_2 ; b) $\text{HS}(\text{CH}_2)_3\text{SH}$, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , $-78^\circ\text{C} \rightarrow \text{RT}$, 99% over two steps; c) $\text{SO}_3 \cdot \text{Py}$, DMSO, DIPEA, CH_2Cl_2 , 0°C ; d) KHMDs , $[\text{18}]\text{crown-6}$, $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, Br_2 , THF, 96% over two steps; e) DIBAL-H , CH_2Cl_2 , -45°C , 99%; f) MsCl , Et_3N , DMAP, CH_2Cl_2 , then LiBr , DMF, 70%; g) LiBHET_3 , THF, 0°C , 99%. DMSO = dimethyl sulfoxide, DIPEA = diisopropylethylamine, Py = pyridine, HMDS = bis-(trimethylsilyl)amide, DIBAL-H = diisobutylaluminum hydride, MsCl = methanesulfonyl chloride, DMAP = 4-dimethylaminopyridine, DMF = *N,N*-dimethylformamide.

Parikh–Doering oxidation, followed by a Horner–Wadsworth–Emmons reaction between the resulting aldehyde and the brominated Still–Gennari phosphonate,^[17] prepared in situ, and produced the kinetic bromoalkene **9** as only one detectable olefin isomer. This high stereoselectivity was critical for our planned formation of the C29–C30 unsymmetrical trisubstituted alkene through a vinylic carbon–carbon σ bond construction.^[6c] However, this approach also necessitated the subsequent removal of the ester functionality. Reduction of **9** to the primary alcohol **10** gave highest yields with DIBAL-H in CH_2Cl_2 , and of the various methods to effect deoxygenation,^[18] treatment of the allylic bromide **11** with Super Hydride was the most effective for synthesis of the desired C29–C32 vinyl bromide. Overall, this robust approach to the central dianion equivalent **4** provided ready access to gram quantities of material ready for coupling to the respective electrophiles **5** and **6**.

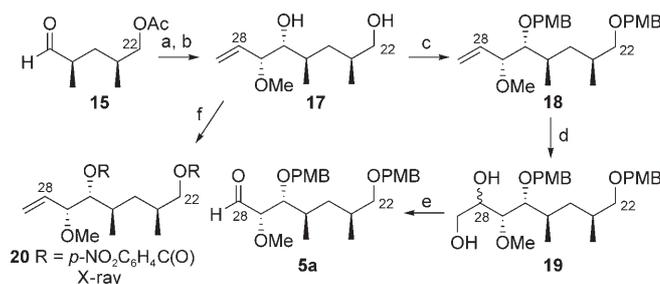
For the synthesis of the C22–C28 electrophile **5**, we required large amounts of the enantiomerically enriched *syn*-1,3-dimethylated alcohols **13** and **14**. For this purpose, we selected enzymatic desymmetrization^[19,20] of the *meso* diol **12**^[21] which gave **13** in consistently high *ee* (96 to 99%).^[22] The resulting monoacetylated product **13** could then be readily converted into the PMB analogue **14** through simple and high-yielding protecting-group manipulations. Both **13** and **14** were cleanly oxidized to the corresponding aldehydes **15** and **16** under Parikh–Doering conditions (Scheme 3).

As the stereochemical configuration of the C26 alcohol is ultimately of no consequence, we elected to pursue two concurrent approaches for the synthesis of the C22–C28 electrophile (Schemes 4 and 5). In the first approach, asymmetric Brown alkoxyallylation,^[23] followed by cleavage of the acetate protecting group to facilitate purification, afforded the diastereomerically pure diol **17**. The facial selectivity of the alkoxyallylation was confirmed by X-ray analysis of the bis-*p*-nitrobenzoate ester (**20**). Although the yield for these two steps was lower than desired, the reaction employs the product from enzymatic desymmetrization directly, can be performed on a large scale, and easily affords



Scheme 3. Reagents and conditions: a) Lipase PS-30 (8 wt%), DME/vinyl acetate (5:1), room temperature, 14 h, 75%, 96–99% *ee*; b) TBSCl, Im, CH_2Cl_2 ; c) K_2CO_3 , MeOH; d) NaH, PMBCL, TBAI, THF; e) TBAF, THF, 90% over four steps; f) $\text{SO}_3 \cdot \text{Py}$, DMSO, DIPEA, CH_2Cl_2 , 0°C , 99% for both **13** and **14**. Im = imidazole, TBA = tetrabutylammonium.

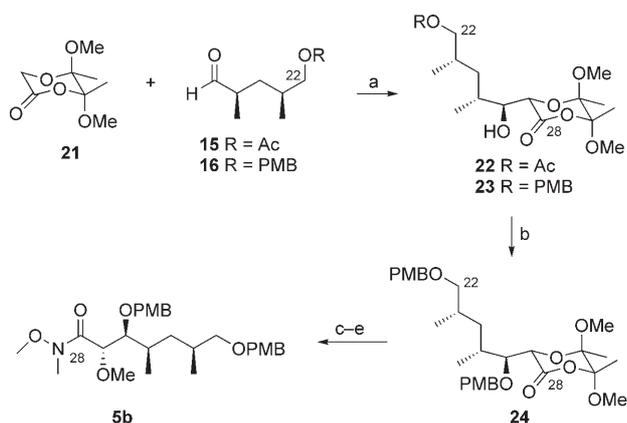
gram quantities of material. Moreover, by masking the C28 carbonyl as an olefin, protection of the C26 alcohol as its PMB ether was facile. In the event, subjecting **17** to standard conditions readily afforded the bis-protected derivative **18**. Direct ozonolysis of **18** proved problematic, thus, we employed a two-step dihydroxylation/cleavage protocol to afford the desired electrophile **5a** in good yield. This approach had the added benefit of avoiding purification of the sensitive α -chiral aldehyde **5a**, as cleavage of **19** with $\text{Pb}(\text{OAc})_4$ was exceptionally clean and high yielding (Scheme 4). The second higher-yielding approach for con-



Scheme 4. Reagents and conditions: a) *s*BuLi, allylmethyl ether, THF, -78°C , then $(-)-(\text{MeO})\text{BIPC}_2$, then $\text{BF}_3 \cdot \text{OEt}_2$, then **15**, 14 h, then 3 *N* NaOH, 30% H_2O_2 , $-78^\circ\text{C} \rightarrow \text{RT}$; b) K_2CO_3 , MeOH, room temperature, 40% over two steps; c) NaH, PMBCL, TBAI, DMF, room temperature, 99%; d) OsO_4 , NMO, acetone/water, room temperature, 78%; e) $\text{Pb}(\text{OAc})_4$, PhH, 99%; f) *p*- $\text{NO}_2\text{C}_6\text{H}_4\text{C}(\text{O})\text{Cl}$, Et_3N , DMAP, CH_2Cl_2 , 99%. Ipc = isopinocampheyl, NMO = *N*-methylmorpholine *N*-oxide.

struction of the C26–C27 carbon bond involved application of our recently developed butane-2,3-diacetal (BDA, **21**) variant of glycolic acid^[24] to effect a highly selective aldol condensation with either **15** or **16** in 82 and 92% yield, respectively (Scheme 5).

An X-ray diffraction experiment performed on a derivative of adduct **22** confirmed that the *R,R*-configured lactone **21** led to the desired stereochemistry of **22**,^[24] however, difficulties with protecting groups precluded the further elaboration of this intermediate. In contrast, the use of PMB-protected derivative **23** proved advantageous for further manipulation, although, as expected, protection of the secondary alcohol at C26 was extremely difficult as a result of the β disposition of the ester carbonyl and numerous acetal moieties present within **23**. Extensive experimentation was ultimately successful in identifying conditions^[25] that allowed



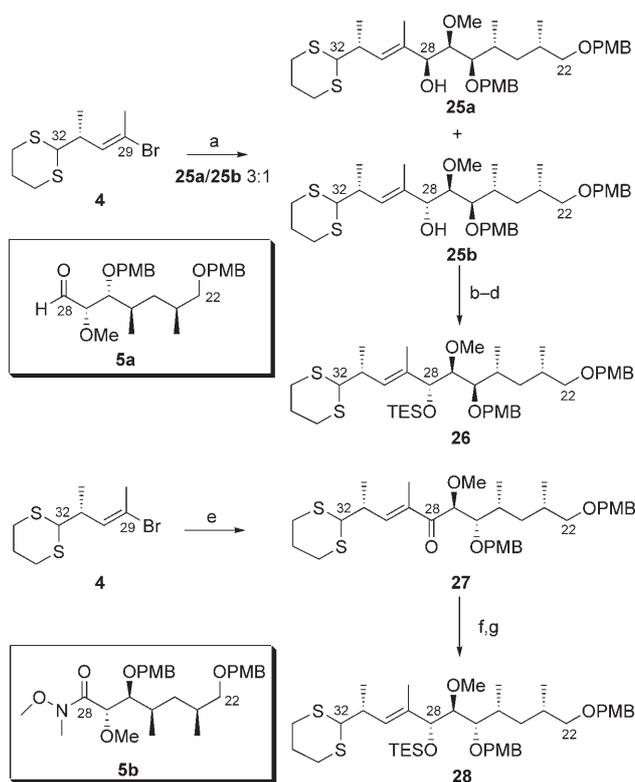
Scheme 5. Reagents and conditions: a) LiHMDS, THF, -78°C , then AcOH, 82% for **15**, 92% for **16**; b) PMB-TCA, TrBF_4 (5 mol%), THF, room temperature, 47%; c) CSA, MeOH, room temperature, 80%; d) Ag_2O , MeI, CH_2Cl_2 , 50°C , 74%; e) LiHMDS, $\text{MeO}(\text{Me})\text{NH}\cdot\text{HCl}$, THF, $-20^{\circ}\text{C} \rightarrow -10^{\circ}\text{C}$, 97%. Tr = trityl; TCA = trichloroacetimidate; CSA = (\pm)-camphorsulfonic acid.

for introduction of the PMB ether (**24**). Although this reaction did not go to completion, the starting material **23** could be recovered and recycled. Transesterification with concurrent liberation of the hydroxy group at C27 was effected by treatment of **24** with catalytic CSA in MeOH.^[24] Finally, methylation under mild silver oxide conditions, followed by formation of the Weinreb amide, concluded a viable route to our second C22–C28 electrophilic coupling partner **5b** (Scheme 5).

Control studies with D_2O quenching indicated that the C29–C32 vinyl bromide **4** could be cleanly transmetalated with *t*BuLi at low temperature (-96°C), and no evidence of abstraction of the C32 dithiane proton was observed. Although an excess (2 equiv) of the lithio anion of **4** was required for improved yields, addition of solutions of either **5a** or **5b** resulted in the desired C–C bond formation between the two coupling partners (Scheme 6).

For **5a**, a partially separable mixture of diastereomers (**25a/25b** 3:1) was obtained in favor of the undesired configuration of the C28 carbinol. This finding was ultimately immaterial as the mixture of diastereomers could be cleanly oxidized to the corresponding ketone and subsequently reduced in high selectivity with $\text{Zn}(\text{BH}_4)_2$ to afford the correct stereochemistry.^[5d,23] Interestingly, relative to other reports (and other substrates in our synthesis; see below) this reduction was very sluggish and it proved surprisingly difficult to remove residual zinc from the product. Finally TES protection at low temperature afforded the completed C22–C32 fragment **26** ready for coupling to the C33–C42 epoxide **6** (Scheme 6).

The addition reaction between **4** and Weinreb amide **5b** under identical conditions afforded a significantly improved yield of the desired coupling partner **27** without the problems of a diastereomeric mixture. In contrast to previous results, subsequent reduction with $\text{Zn}(\text{BH}_4)_2$ was rapid but still occurred with high selectivity and yield. The variation in reactivity must originate either through direct interaction of the C26 alkoxy function or perhaps indirectly through a

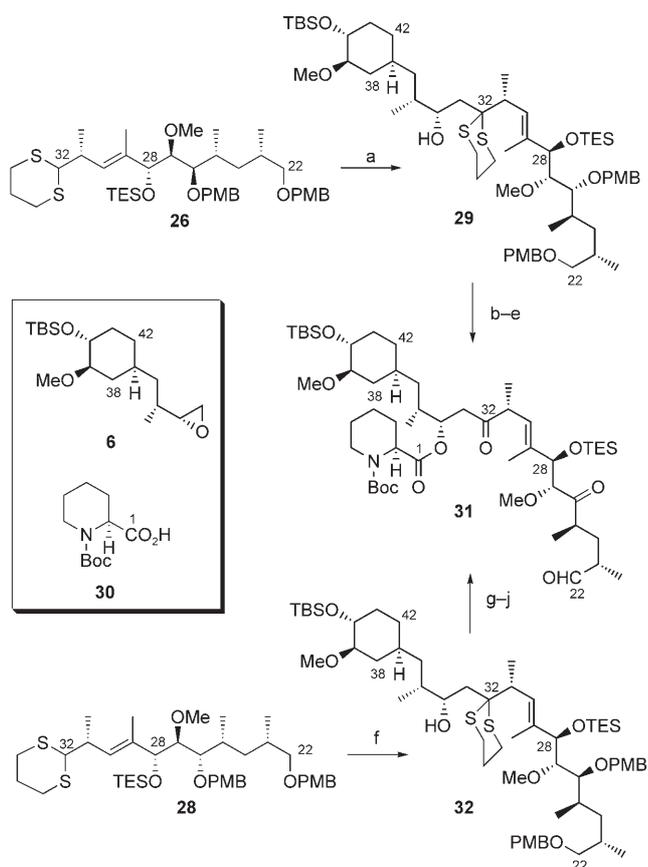


Scheme 6. Reagents and conditions: a) *t*BuLi, THF, -96°C , then **5a**, $-96^{\circ}\text{C} \rightarrow -78^{\circ}\text{C}$, 66% (**25a/25b** 3:1); b) $\text{SO}_3\cdot\text{Py}$, DMSO, DIPEA, CH_2Cl_2 , 0°C , 99%; c) $\text{Zn}(\text{BH}_4)_2$, Et_2O , -20°C , 3 days, 80%; d) TESOTf, 2,6-lut, CH_2Cl_2 , -78°C , 40 min, 99%; e) *t*BuLi, THF, -96°C , then **5b**, $-96^{\circ}\text{C} \rightarrow -78^{\circ}\text{C}$, 80%; f) $\text{Zn}(\text{BH}_4)_2$, Et_2O , -20°C , 2 h, 83%; g) TESCl, Im, DMF, 50°C , 93%. 2,6-lut = 2,6-lutidine, TESOTf = triethylsilyl trifluoromethanesulfonate.

conformational change induced by the opposite stereochemistry at this center. Differences were once again apparent in the following TES protection, which was extremely sluggish with TESOTf even at room temperature. Switching to TESCl in DMF with heating resolved this issue and afforded a second completed C22–C32 fragment **28** ready for coupling to the epoxide **6** (Scheme 6).

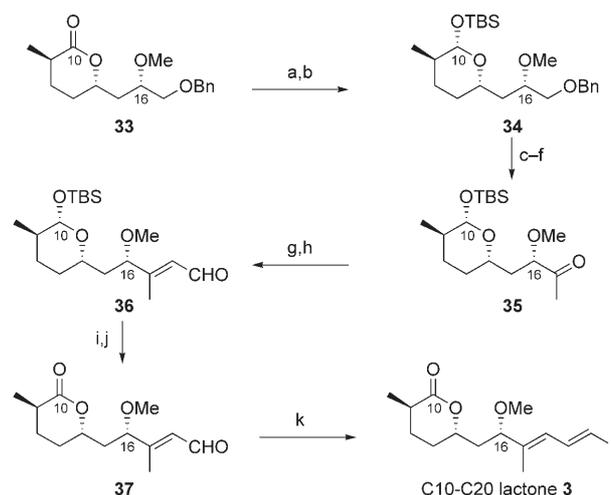
We had previously disclosed our approach^[27] to the latter C33–C42 epoxide **6** which highlighted the intramolecular trapping of oxonium ions by allyl silanes.^[28] Addition of *t*BuLi to a cold (-78°C) mixture of **6** and **26**, or **28**, in THF/HMPA followed by rapid warming to -40°C resulted in smooth epoxide ring opening and construction of the C22–C42 carbon framework.^[6c] For dithiane **28**, it was important to slightly decrease the amount of HMPA and the reaction time to maximize the yield. Removal of the dithiane moiety in both **29** and **32** using the Stork–Zhao bis(trifluoroacetoxy)iodobenzene protocol^[29] occurred smoothly and was necessary to permit esterification of the C34 alcohol of **29** and **32** with (*S*)-Boc-pipecolic acid. PMB deprotection with buffered DDQ, followed by double oxidation at C26 and C22 employing Swern conditions, afforded in excellent yield the common intermediate **31**, which was identical in all respects (NMR, MS, IR, $[\alpha]_D$) starting from either **29** or **32**. The use of Swern

oxidation conditions was critical to avoid formation of the undesired lactone between C22 and C26-OH (Scheme 7).^[30]



Scheme 7. Reagents and conditions: a) **6**, *t*BuLi, THF/HMPA (5:1), $-78^{\circ}\text{C} \rightarrow -40^{\circ}\text{C}$, 77%; b) THF/MeOH/H₂O (10:9:1), PhI(OCOCF₃)₂, room temperature, 84%; c) **30**, DCC, DMAP, CH₂Cl₂, -5°C , 24 h, 84%; d) DDQ, pH 7 buffer, CH₂Cl₂, room temperature, 93%; e) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, 99%; f) **6**, *t*BuLi, THF/HMPA (9:1), $-78^{\circ}\text{C} \rightarrow -40^{\circ}\text{C}$, 81%; g) PhI(OCOCF₃)₂, THF/MeOH/H₂O (10:9:1), room temperature, 83%; h) **30**, DCC, DMAP, CH₂Cl₂, -5°C , 24 h, 99%; i) DDQ, pH 7 buffer, CH₂Cl₂, room temperature, 90%; j) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, 99%. HMPA = hexamethylphosphoramide, DCC = 1,3-dicyclohexylcarbodiimide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Boc = *tert*-butyloxycarbonyl.

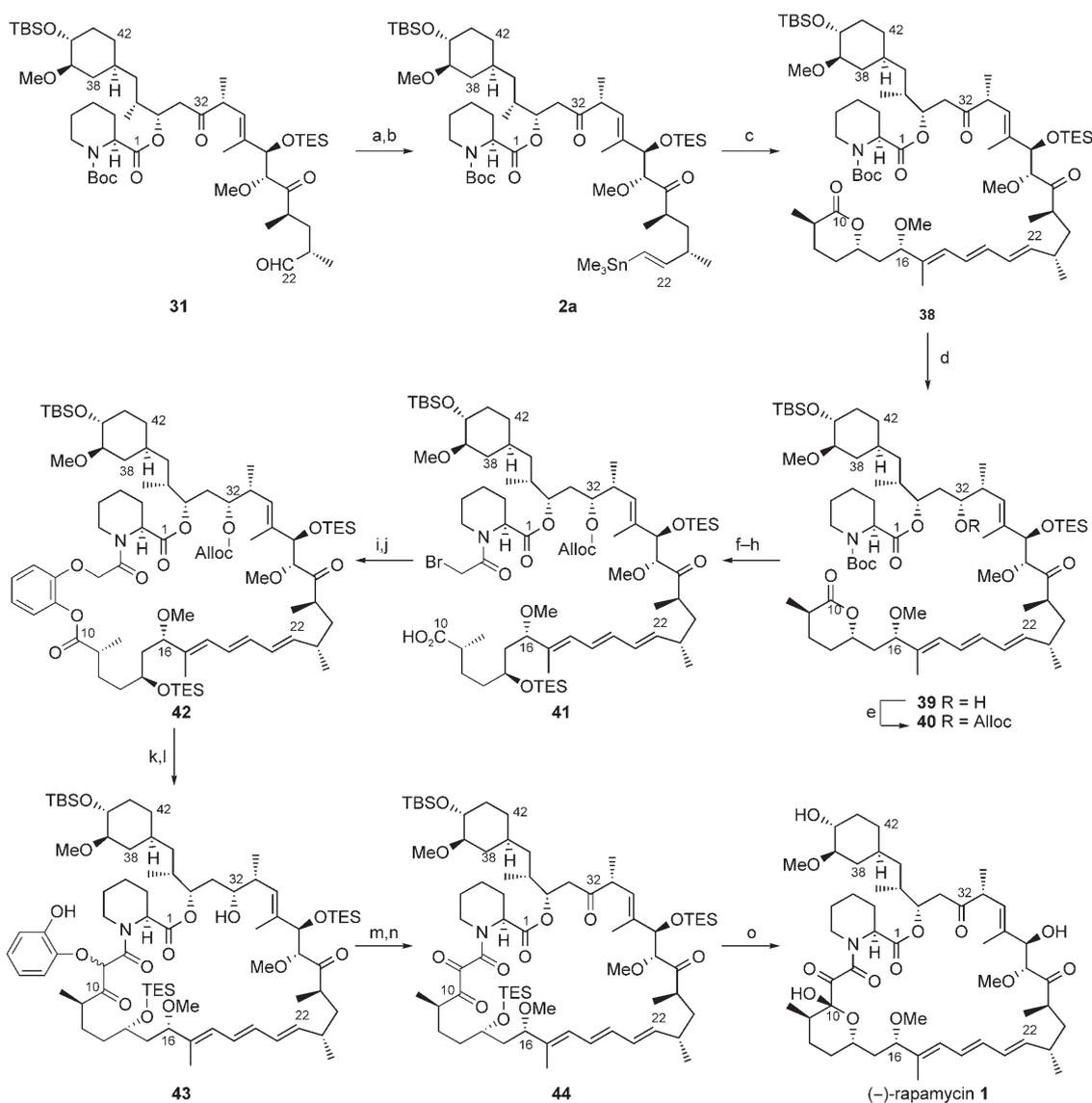
Our synthesis of an advanced intermediate for the preparation of the C10–C20 lactone **3** has also been described and highlights the utility of iron carbonyl methodology for the construction of complex molecules such as lactone **33**.^[31] Previous results^[32] concerning construction of the triene portion of rapamycin had suggested that a Stille coupling^[33] would be the best approach for coupling to the C21–C42 fragment. Furthermore, model studies within our group indicated disconnection at the C20–C21 bond was optimal, and in accordance with the observations of Smith et al.^[5b] we elected to employ the lactone portion of the molecule as the vinyl iodide. The C11 methyl stereocenter proved extremely susceptible to epimerization and necessitated reduction to the lactol followed by protection as the TBS ether **34** (Scheme 8).



Scheme 8. Reagents and conditions: a) DIBAL-H, toluene, -78°C ; b) TBSCl, Im, DMAP, DMF, room temperature, 92% over two steps; c) Pd(OH)₂, H₂, EtOAc, room temperature, 99%; d) TPAP, NMO, 4-Å M.S., CH₂Cl₂/CH₃CN, room temperature, 99%; e) MeMgBr, THF, -78°C , 74% (d.r. = 2:1); f) TPAP, NMO, 4-Å M.S., CH₂Cl₂/CH₃CN, room temperature, 92%; g) (EtO)₂P(O)CH₂CN, NaHMDS, THF, 0°C , then ketone **35**, -78°C , 85% (*E/Z* 7:1); h) DIBAL-H, toluene, -78°C , 91%; i) TBAF, AcOH/H₂O/THF, room temperature; j) TPAP, NMO, 4-Å M.S., CH₂Cl₂, 85% over two steps; k) CrCl₂, CHI₃, THF/dioxane, 0°C , 80% (*E/Z* 6:1). TPAP = tetra-*n*-propylammonium perruthenate, M.S. = molecular sieves, Bn = benzyl.

Debenzylation of **34** with Pearlman's catalyst, TPAP^[34] oxidation, and addition of MeMgBr into the resulting aldehyde gave the desired secondary alcohol as a 2:1 mixture of diastereomers. A second oxidation with TPAP then afforded ketone **35** for introduction of the C17–C18 alkene. Homologation was then accomplished with commercially available diethyl(cyanomethyl)phosphonate,^[35] which at low temperature (-78°C) gave good levels of *E/Z* olefin geometry (7:1) for the conjugated product as established by NOE studies. Importantly, the major isomer could be separated and subsequently reduced cleanly with DIBAL-H to afford the corresponding enal **36**. Desilylation of **36** with TBAF in the presence of AcOH,^[36] followed by oxidation of the resulting lactol with TPAP, gave lactone **37** which was then subjected to a Takai olefination^[37] using the modified conditions reported by Evans and Black.^[38] The resulting vinyl iodide **3** was formed as an inseparable mixture of olefin isomers (6:1) in favor of the desired *E* configuration (Scheme 8).

The C21–C42 vinyl stannane was constructed through a second Takai olefination, and proceeded smoothly to give the *E*-vinyl iodide with no observable formation of the *Z* isomer (Scheme 9). Cross-coupling with freshly prepared [Pd-(PFur)₂Cl₂]^[39] and hexamethyltin afforded the desired vinyl stannane **2a**. A second coupling reaction with the same catalyst system and the *E/Z* isomeric mixture of lactones **3** effectively generated the desired triene **38**. Interestingly, no minor geometric isomers could be detected in the ¹H NMR spectrum of the Stille coupled product. One explanation of this fortuitous result is that the minor *Z* component of **3** might have equilibrated to the *E* isomer under the reaction conditions. Alternatively, the *Z* isomer may react more slowly



Scheme 9. Reagents and conditions: a) CrCl_2 , CH_3 , THF, $0^\circ\text{C} \rightarrow \text{RT}$, 82%; b) $[\text{Pd}(\text{PFur}_3)_2\text{Cl}_2]$, $(\text{Me}_3\text{Sn})_2$, NMP, dark, room temperature, 68%; c) $[\text{Pd}(\text{PFur}_3)_2\text{Cl}_2]$, **3**, NMP, dark, room temperature, 69%; d) $\text{LiAlH}(\text{O}t\text{Bu})_3$, THF, -10°C , 81%; e) Alloc-Cl, 4-pyrrolidinopyridine, CH_2Cl_2 , 81%; f) 0.1 M LiOH in H_2O , THF, 0°C , 89%; g) TESOTf, 2,6-lut, CH_2Cl_2 , $-20^\circ\text{C} \rightarrow \text{RT}$, 88%; h) $\text{BrCH}_2\text{CO}_2\text{Br}$, 2,6-lut, CH_2Cl_2 , -20°C , 66%; i) catechol, DCC, DMAP, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{RT}$, 88%; j) K_2CO_3 , DMF, room temperature, 81%; k) LiHMDS, THF, $-78^\circ\text{C} \rightarrow -20^\circ\text{C}$, 78%; l) $[\text{Pd}(\text{PPh}_3)_4]$, dimedone, THF, room temperature, 80%; m) $\text{PhI}(\text{OAc})_2$, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (10:1), 0°C ; n) DMP, Py, CH_2Cl_2 , room temperature, 61% over two steps; o) HF-Py, THF, 50°C , 61%. Fur = 2-furyl, NMP = *N*-methyl pyrrolidone, Alloc-Cl = allyloxycarbonyl chloride.

than the *E* isomer. To avoid recurring problems with β elimination across C33–C34 later in the synthesis, the C32 carbonyl was selectively reduced at this point with $\text{LiAlH}(\text{O}t\text{Bu})_3$ ^[40] to afford **39**, which was subsequently protected with Alloc-Cl (**40**). Further manipulation to α -bromoamide **41** was achieved by hydrolysis of the lactone to the carboxylic acid, protection of the resulting secondary alcohol with concomitant liberation of the secondary amine, and finally amide formation with α -bromoacetyl bromide. This sequence of events was critical to avoid epimerization of the C11 methyl stereocenter.

DCC-mediated coupling of catechol with the free carboxylic acid **41**, followed by alkylative ring closure afforded the macrocyclic ether **42** in 71% overall yield. We were especially

pleased that the catechol tethering strategy employing an uncommon macroetherification^[41] was demonstrated after treatment of **42** with LiHMDS effected the templated Dieckmann-like condensation^[42] to construct the C9–C10 bond. Following Alloc deprotection, **43** was isolated in good yield. Finally, catechol cleavage, oxidation of the C9 and C32 alcohols (**44**), and silyl group deprotection resulted in spontaneous C10 lactol formation to complete the total synthesis of rapamycin (**1**), which was identical in all respects by comparison with an authentic sample of the natural product.

In summary, we have presented a new and efficient convergent route to an intriguing natural product, whose applications continue to evolve to this day. The challenge

posed by the total synthesis of (–)-rapamycin has been met through a combination of established research procedures and our own methods. The use of BDA chemistry as both a protecting and stereodirecting functionality, iron carbonyl chemistry, intramolecular trapping of oxonium ions by allyl silanes, and an efficient macroetherification/catechol tethering strategy for the formation of the formidable macrocyclic core of rapamycin represent some of the highlights from this approach.

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- [1] a) C. Vezina, A. Kudelski, S. N. Sehgal, *J. Antibiot.* **1975**, 28, 721; b) S. N. Sehgal, H. Baker, C. Vezina, *J. Antibiot.* **1975**, 28, 727.
- [2] For structure determination, see: a) D. C. N. Swindells, P. S. White, J. A. Findlay, *Can. J. Chem.* **1978**, 56, 2491; b) J. A. Findlay, L. Radics, *Can. J. Chem.* **1980**, 58, 579; c) J. A. Findlay, L. Radics, *Can. J. Chem.* **1981**, 59, 49; d) J. B. McAlpine, S. J. Swanson, M. Jackson, D. N. Whittern, *J. Antibiot.* **1991**, 44, 688.
- [3] R. R. Martel, J. Klicius, S. Galet, *Can. J. Physiol. Pharmacol.* **1977**, 55, 48.
- [4] a) R. Y. Calne, S. Lim, A. Samaan, D. S. J. Collier, S. G. Pollard, D. J. White, *Lancet* **1989**, 2, 227; b) B. D. Kahan, J. Podbielski, K. L. Napoli, S. M. Katz, H.-U. Meier-Kriesche, C. T. Van Buren, *Transplantation* **1998**, 66, 1040.
- [5] See: a) A. B. Smith, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1997**, 119, 947; b) A. B. Smith, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1997**, 119, 962; c) A. B. Smith, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1995**, 117, 5407; d) C. M. Hayward, D. Yohannes, S. J. Danishefsky, *J. Am. Chem. Soc.* **1993**, 115, 9345; e) D. Romo, S. D. Meyer, D. D. Johnson, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, 115, 7906; f) K. C. Nicolaou, A. D. Piscopio, P. Bertinato, T. K. Chakraborty, N. Minowa, K. Koide, *Chem. Eur. J.* **1995**, 1, 318; g) K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, 115, 4419, and references therein.
- [6] For reviews, see: a) A. Farooq, S. Anjum, M. I. Choudhary, A.-U. Rahman, *Curr. Org. Chem.* **1998**, 2, 281; b) M. C. Norley, *Contemp. Org. Syn.* **1996**, 3, 345; c) A. B. Smith, S. M. Condon, J. A. McCauley, *Acc. Chem. Res.* **1998**, 31, 35.
- [7] See: R. E. Ireland, J. L. Gleason, L. D. Gegnas, T. K. Highsmith, *J. Org. Chem.* **1996**, 61, 6856, and references therein.
- [8] a) C. Allen, Y. Yu, D. Maysinger, A. Eisenberg, *Bioconjugate Chem.* **1998**, 9, 564; b) L. A. Greene, A. S. Tischler, *Proc. Natl. Acad. Sci. USA* **1976**, 73, 2424.
- [9] G. M. Salituro, D. L. Zink, A. Dahl, J. Nielsen, E. Wu, L. Huang, C. Kastner, F. J. Dumont, *Tetrahedron Lett.* **1995**, 36, 997.
- [10] See: a) K. Baumann, K. Hoegenauer, H. Knapp, M. Bacher, A. Steck, T. Wagner, *Tetrahedron* **2005**, 61, 4819; b) P. Nussbaumer, M. A. Grassberger, G. Schulz, *Tetrahedron Lett.* **1999**, 40, 3869.
- [11] a) D. E. A. Brittain, C. M. Griffith-Jones, M. R. Linder, M. D. Smith, C. McCusker, J. S. Barlow, R. Akiyama, K. Yasuda, S. V. Ley, *Angew. Chem.* **2005**, 117, 2792; *Angew. Chem. Int. Ed.* **2005**, 44, 2732; b) T. Fehr, J.-J. Sanglier, W. Schuler, L. Gschwind, M. Ponelle, W. Schilling, C. Wioland, *J. Antibiot.* **1996**, 49, 230.
- [12] For reviews related to biological aspects, see: a) S. N. Sehgal, K. Molnar-Kimber, T. D. Ocain, B. M. Weichman, *Med. Res. Rev.* **1994**, 14, 1; b) W. Braun, J. Kallen, V. Mikol, M. D. Walkinshaw, K. Wüthrich, *FASEB J.* **1995**, 9, 63; c) P. J. Belshaw, S. D. Meyer, D. D. Johnson, D. Romo, Y. Ikeda, M. Andrus, D. G. Alberg, L. W. Schultz, J. Clardy, S. L. Schreiber, *Synlett* **1994**, 391; d) G. S. Hamilton, J. P. Steiner, *J. Med. Chem.* **1998**, 41, 5119.
- [13] For a review regarding rapamycin derivatives (CCI-779, RAD001, and AP23573), see: S. Vignot, S. Faivre, D. Aguirre, E. Raymond, *Ann. Oncol.* **2005**, 16, 525, and references therein.
- [14] For reviews on mTOR inhibitors, see: a) S. Wullschlegel, R. Loewith, M. N. Hall, *Cell* **2006**, 124, 471; b) S. Huang, J. Houghton, *Curr. Opin. Pharmacol.* **2003**, 3, 371; c) P. Molewski, *Anti-Cancer Drugs* **2006**, 17, 487; d) S. Faivre, G. Kroemer, E. Raymond, *Nat. Rev. Drug Discovery* **2006**, 5, 671; e) P. E. Wallemacq, *Expert Opin. Invest. Drugs* **1996**, 5, 225.
- [15] For reviews of mTOR, see: a) D. C. Fingar, J. Blenis, *Oncogene* **2004**, 23, 3151; b) N. Hay, N. Sonenberg, *Genes Dev.* **2004**, 18, 1926.
- [16] G. Ehrlich, M. Kalesse, *Synlett* **2005**, 4, 655.
- [17] By modification of: a) F.-L. Qing, X. Zhang, *Tetrahedron Lett.* **2001**, 42, 5929; see also: b) K. Tago, H. Kogen, *Org. Lett.* **2000**, 2, 1975; c) T. Olpp, R. Brückner, *Synthesis* **2004**, 13, 2135.
- [18] See: W. Hartwig, *Tetrahedron* **1983**, 39, 2609, and references therein.
- [19] J. C. Anderson, S. V. Ley, S. P. Marsden, *Tetrahedron Lett.* **1994**, 35, 2087.
- [20] A. K. Ghosh, X. Xu, *Org. Lett.* **2004**, 6, 2055.
- [21] E. Prusov, H. Röhm, M. E. Maier, *Org. Lett.* **2006**, 8, 1025.
- [22] Enantiomeric excesses were determined by HPLC analysis (CHIRALCEL OD, 98:2 Hex/iPrOH, 0.5 mL min⁻¹, 25 °C; *rt*_(minor) = 17.2 min, *rt*_(major) = 22.6 min) of the benzoate ester.
- [23] H. C. Brown, P. K. Jadhav, K. S. Bhat, *J. Am. Chem. Soc.* **1988**, 110, 1535.
- [24] S. V. Ley, D. J. Dixon, R. T. Guy, M. A. Palomero, A. Polara, F. Rodriguez, T. D. Sheppard, *Org. Biomol. Chem.* **2004**, 2, 3618.
- [25] a) N. Nakajima, K. Horita, R. Abe, O. Yonemitsu, *Tetrahedron Lett.* **1988**, 29, 4139; b) I. Paterson, D. Y.-K. Chen, M. J. Coster, J. L. Aceña, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson, R. D. Norcross, *Angew. Chem.* **2001**, 113, 4179; *Angew. Chem. Int. Ed.* **2001**, 40, 4055.
- [26] a) T. Nakata, T. Tanaka, T. Oishi, *Tetrahedron Lett.* **1983**, 24, 2653; b) S. Pikul, J. Raczko, K. Ankner, J. Jurczak, *J. Am. Chem. Soc.* **1987**, 109, 3981.
- [27] a) S. V. Ley, C. Kouklovsky, *Tetrahedron* **1994**, 50, 835; b) C. Kouklovsky, S. V. Ley, S. P. Marsden, *Tetrahedron Lett.* **1994**, 35, 2091.
- [28] For a review, see: D. Schinzer, *Synthesis* **1988**, 263.
- [29] G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, 30, 287.
- [30] For examples of Swern bis-oxidations, see: a) S. C. Howell, S. V. Ley, M. Mahon, P. A. Worthington, *J. Chem. Soc. Chem. Commun.* **1981**, 507; b) D. M. Hollinshead, S. C. Howell, S. V. Ley, M. Mahon, N. M. Ratcliffe, P. A. Worthington, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1579; c) R. Chênevert, G. Courchesne, D. Caron, *Tetrahedron: Asymmetry* **2003**, 14, 2567.
- [31] a) S. V. Ley, J. Norman, C. Pinel, *Tetrahedron Lett.* **1994**, 35, 2095; b) for a review, see: S. V. Ley, L. R. Cox, G. Meek, *Chem. Rev.* **1996**, 96, 423.
- [32] See, for example: a) A. D. Piscopio, N. Minowa, T. K. Chakraborty, K. Koide, P. Bertinato, K. C. Nicolaou, *J. Chem. Soc. Chem. Commun.* **1993**, 617; b) A. B. Smith, S. M. Condon, J. A. McCauley, J. W. Leahy, J. L. Leazer, Jr., R. E. Maleczka, *Tetrahedron Lett.* **1994**, 35, 4907.
- [33] T. N. Mitchell, *Synthesis* **1992**, 803.
- [34] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.
- [35] For other examples of use of this reagent with ketones that have an α -hydroxy functionality, see: a) T. Tsukuda, I. Umeda, K.

- Masubuchi, M. Shirai, N. Shimma, *Chem. Pharm. Bull.* **1993**, *41*, 1191; b) S. Jendrzejewski, P. Ermann, *Tetrahedron Lett.* **1993**, *34*, 615.
- [36] The addition of AcOH was found to be necessary to prevent epimerization at the C11 stereocenter in the intermediate hydroxy aldehyde.
- [37] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408.
- [38] D. A. Evans, W. C. Black, *J. Am. Chem. Soc.* **1993**, *115*, 4497.
- [39] C. M. Hettrick, W. J. Scott, *J. Am. Chem. Soc.* **1991**, *113*, 4903.
- [40] The stereochemistry of this reduction was confirmed by preparing a cyclic acetonide and analysis of its ¹³C NMR spectrum from a retroaldol product from **39**. See: a) D. Yohannes, S. J. Danishefsky, *Tetrahedron Lett.* **1992**, *33*, 7469; b) J. I. Luengo, A. L. Konialian, D. A. Holt, *Tetrahedron Lett.* **1993**, *34*, 991; c) J. I. Luengo, L. W. Rozamus, D. A. Holt, *Tetrahedron Lett.* **1994**, *35*, 6469.
- [41] For examples, see: a) S. Venkatraman, F. G. Njoroge, V. Girijavallabhan, *Tetrahedron* **2002**, *58*, 5453; b) M. N. Masuno, I. N. Pessah, M. M. Olmstead, T. F. Molinski, *J. Med. Chem.* **2006**, *49*, 4497.
- [42] For reviews, see: a) E. V. Gorobets, M. S. Miftakhov, F. A. Valeev, *Russ. Chem. Rev.* **2000**, *69*, 1001; b) D. K. Banerjee, *Proc. Indian Acad. Sci. Sect. A* **1974**, *79*, 282.
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