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Total Synthesis of (+)-SCH 351448: Efficiency via Chemoselectivity and Redox-Economy Powered by Metal Catalysis

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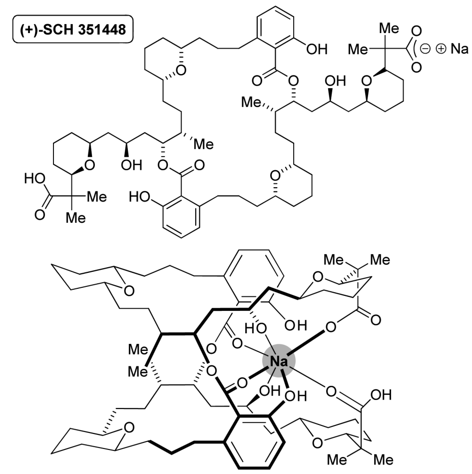
S Supporting Information

ABSTRACT: The polyketide natural product (+)-SCH 351448, a macrodiolide ionophore bearing 14 stereogenic centers, is prepared in 14 steps (LLS). In eight prior syntheses, 22−32 steps were required. Multiple chemoselective and redox-economic functional group interconversions collectively contribute to a step-change in efficiency.

Among the many issues of selectivity that impact chemical synthesis,[1] chemoselectivity (site-selectivity),[2] the ability to discriminate between like or unlike functional groups, and redox-economy[3] have the greatest potential to impact step-economy, which may be considered the primary indicator of strategic efficiency[4] in ideal chemical synthesis.[5] Methods that are chemoselective (site-selective) and redox-economic preclude use of protecting groups and discrete oxidation level adjustments, which for complex molecules may account for over half the steps of a synthetic route even after intensive process optimization.[6−8] Guided by these concepts, we have developed a lexicon of catalytic methods[9] for the direct stereo- and site-selective[9c] conversion of lower alcohols to higher alcohols, as well as related carbonyl reductive couplings mediated by 2-propanol.[9] These methods bypass discrete alcohol-to-carbonyl redox reactions and use of premetalated C-nucleophiles and have been shown to streamline the synthesis of diverse polyketide natural products.[9d]

Here, we sought to deploy multiple chemoselective and redox-economic methods—those developed within and beyond our laboratory—to more broadly demonstrate the impact of redox-economy and chemoselectivity on synthetic efficiency. The type I polyketide (+)-SCH 351448,[10,11] an ionophoric macrodiolide bearing 14 stereogenic centers, is an ideal vehicle for this purpose, as eight elegant prior syntheses are available to serve as benchmarks (Figure 1).[12−14] Previously, 22−32 steps (LLS) were required to construct (+)-SCH 351448. Through the use of methods that embody *exclusive* chemoselectivity (site-selective modification of one functional group in the presence of multiple like/unlike functional groups), *inclusive* chemoselectivity (concomitant modification of multiple like/unlike functional groups), and redox-economy, the synthesis of (+)-SCH 351448 is now achieved in only 14 steps (LLS). An analysis of reaction type for past and present syntheses suggest the accumulation of chemoselective and redox-economic processes manifest in the present route as an increased proportion of skeletal construction events, an outcome that is better aligned with the ideals of synthetic efficiency.[5]



Total or Formal Syntheses	LLS (TS)	Skeletal Assembly	Redox Reactions	Protection-Deprotection	Other Reactions
Lee[b] (ref. 12a,b)	27 (46)	9 (33%)	8 (30%)	7 (26%)	3 (11%)
De Brabander[b] (ref. 12c,d)	22 (41)	7 (32%)	3 (14%)	9 (40%)	3 (14%)
Leighton[b] (ref. 12e)	25 (39)	12 (48%)	6 (24%)	6 (24%)	1 (4%)
Crimmins[b] (ref. 12f)	32 (54)	10 (31%)	7 (22%)	7 (22%)	8 (25%)
Loh[c] (ref. 13a)	23 (48)	10 (43%)	5 (22%)	8 (35%)	0
Rychnovsky[b] (ref. 12g)	24 (48)	6 (25%)	8 (33%)	9 (38%)	1 (4%)
Panek[b] (ref. 12h)	26 (48)	8 (31%)	7 (27%)	9 (34%)	2 (8%)
Hong[c] (ref. 13b)	28 (68)	9 (32%)	6 (21%)	10 (36%)	3 (11%)
Krische[b] (*This Work*)	14 (22)	8 (57%)	3 (21.5%)	3 (21.5%)	0

Figure 1. Type I polyketide (+)-SCH 351448, depiction of the sodium ion binding motif adapted from single crystal X-ray diffraction data and summary of synthetic work including analysis of reaction type.[a] [a] For graphical summaries of prior total syntheses, see Supporting Information. Longest Linear Sequence (LLS); Total Steps (TS). Only transformations in the longest linear sequence (LLS) are considered in the analysis of reaction type. [b] Total syntheses. [c] Formal syntheses.

(+)-SCH 351448, a secondary metabolite of *Micromonospora* sp. bacteria, was identified in connection with a bioassay-guided fractionation aimed at the identification of cholesterol reducing agents.[10] Specifically, (+)-SCH 351448 is an activator of a low density lipoprotein receptor (LDL-R) promoter (IC_{50} = 25 μM). As increased expression of LDL-R decreases blood serum cholesterol levels,[15] (+)-SCH 351448, the first small molecule activator of the LDL-R promoter, has garnered interest from synthetic chemists as a potential starting point for the design of therapeutic agents for the treatment of hypercholesterolemia.[12−14]

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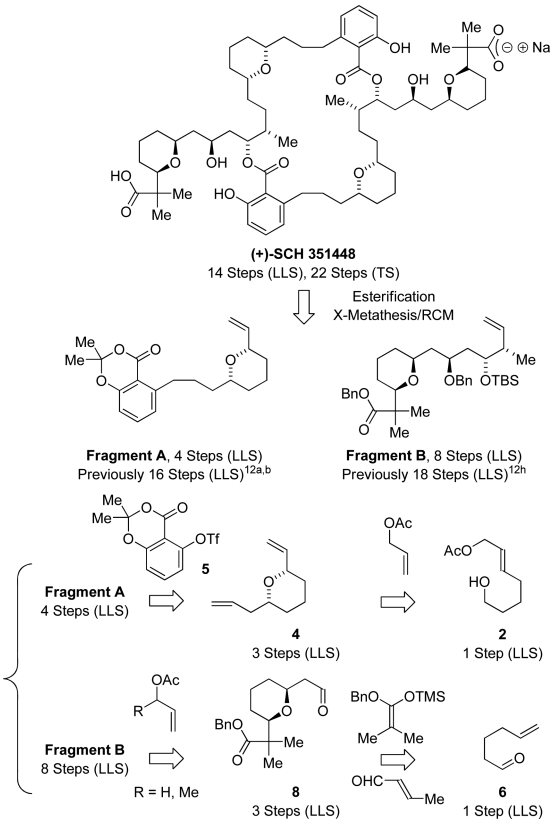
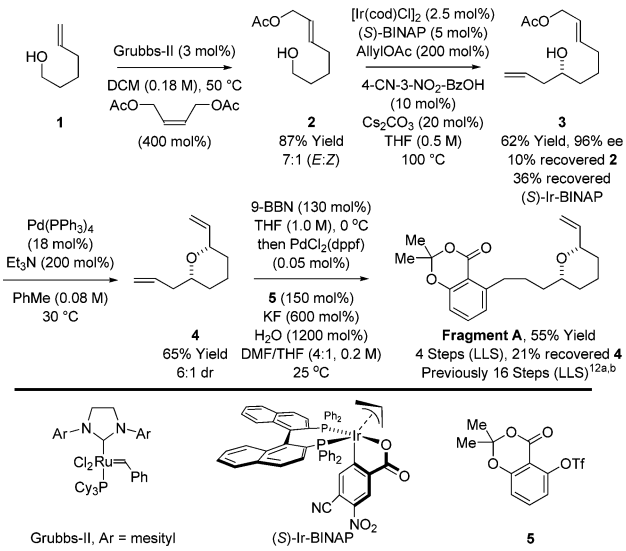
Scheme 1. Retrosynthetic Analysis of (+)-SCH 351448



Our retrosynthetic analysis of (+)-SCH 351448 is as follows (Scheme 1). The symmetric macrodiolide is assembled from Fragments **A** and **B** via esterification and cross-metathesis/ring-closing metathesis (RCM) reactions.[16] For the synthesis of Fragment **A**, four consecutive metal catalyzed reactions are employed: cross-metathesis to form alcohol **2**,[16,19] tandem nucleophilic[17a,b] and electrophilic[18] allylations to convert alcohol **2** to pyran **4**,[19] and the Suzuki cross-coupling of pyran **4** with aryl triflate **5**.[20] Fragment **B** is prepared in eight steps from 5-hexen-1-ol **1**. Key transformations include Kiyooka's variant of the enantioselective Mukaiyama aldol reaction (applied to aldehyde **6**)[21] followed by Fuwa's cascading cross-metathesis-*oxa*-Michael cyclization[22,23] to form pyran **8**, which upon sequential asymmetric transfer hydrogenative allylation[17a,b] and crotylation[17c,d] deliver Fragment **B**. The proposed synthesis of (+)-SCH 351448 exploits several chemoselective and redox-economic transformations. For example, the C−H allylation of alcohol **2** avoids discrete alcohol-to-carbonyl redox reactions and requires chemoselective ionization of allylic carboxylate groups. The hydroboration of pyran **4** requires discrimination between allylic vs homoallylic terminal olefin moieties. The two-step conversion of aldehyde **6** to pyran **8** occurs in the absence of redox reactions, whereas the final step of the synthesis, the concomitant hydrogenation/hydrogenolysis of six functional groups (two olefins, two benzyl ethers, two benzyl esters), represents a redox event that embodies a high degree of inclusive chemoselectivity. Although the endgames differ, it should be noted that Fragments **A** and **B** appear as intermediates in total syntheses by Lee[12a,b] (4 vs 16 steps) and Panek (8 vs 18 steps),[12h] respectively.

Scheme 2. Synthesis of Fragment A Using Four Consecutive Metal Catalyzed Transformations[a]



[a]Yields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis. Identical yields and diastereoselectivities are observed upon use of recovered (*S*)-IrLn in the conversion of **2** to **3**. See Supporting Information for further details.

The synthesis of Fragment **A** is achieved using four consecutive metal catalyzed transformations (Scheme 2). Cross-metathesis of 5-hexen-1-ol **1** with *cis*-1,4-diacetoxy-2-butene[19] using the second generation Grubbs catalyst[16,24] delivers the allylic acetate **2** in 87% yield as a 7:1 mixture of alkene *E*/*Z* stereoisomers. Transfer hydrogenative *C*-allylation of allylic acetate **2** using allyl acetate as the allyl donor provides the homoallylic alcohol **3** in 62% yield and 96% enantiomeric excess. Here, chemoselective activation of allylic acetates is achieved by virtue of the fact that the stability of a late transition metal−olefin π-complex decreases with increasing degree of olefin substitution.[25] Tsuji−Trost cyclization[18] converts the homoallylic alcohol **3** to the 2,6-*cis*-disubstituted pyran **4** with good levels of diastereoselectivity, as determined by ^{1}H NMR analysis.[19] The Suzuki cross-coupling of pyran **4** with aryl triflate **5** requires chemoselective hydroboration of allylic vs homoallylic ethers. Due to the negative inductive effect of the pyran oxygen, the alkene moiety of the homoallylic ether undergoes selective hydroboration with 9-BBN, enabling formation of Fragment **A** in 55% yield, along with a 21% yield of recovered pyran **4**. Thus, Fragment **A**, previously made in 16 steps (LLS),[12a,b] is now made in four steps (LLS).

The synthesis of Fragment **B** begins with Moffatt−Swern oxidation of 5-hexen-1-ol **1** (Scheme 3).[26] The resulting aldehyde **6** is subjected to Kiyooka's variant of the enantioselective Mukaiyama aldol reaction[21] to furnish the neopentyl alcohol **7** in 70% yield and 93% ee. In alignment with Fuwa's observations,[22,23] cross-metathesis of unsaturated alcohol **7** with crotonaldehyde in the presence of substoichiometric quantities of (*S*)-camphorsulfonic acid using the second-generation Hoveyda−Grubbs catalyst occurs with spontaneous *oxa*-Michael cyclization to furnish the 2,6-disubstituted pyran **8** as a single diastereomer, as determined by ^{1}H NMR analysis. Exposure of aldehyde **8** to conditions for allylation via 2-propanol mediated transfer hydrogenation enabled formation of homoallylic alcohol **9**, which upon benzylation and

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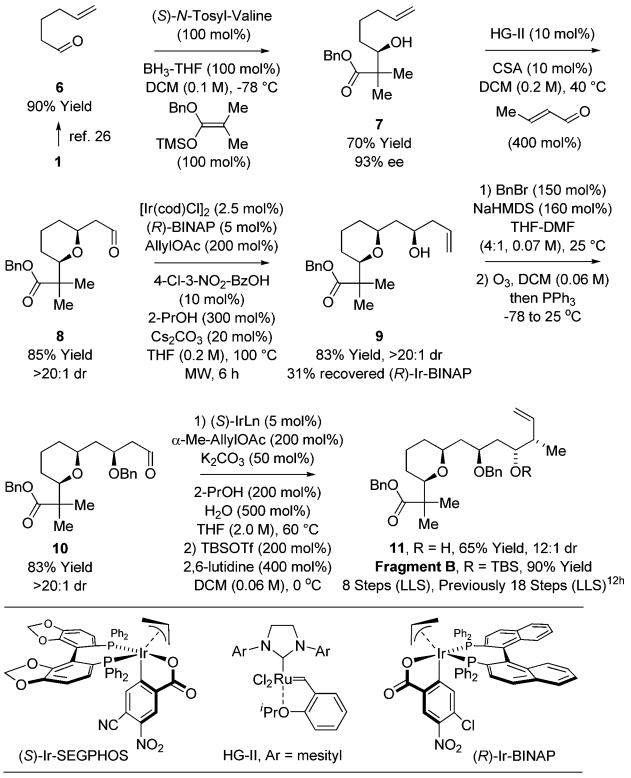
Scheme 3. Synthesis of Fragment B[a]



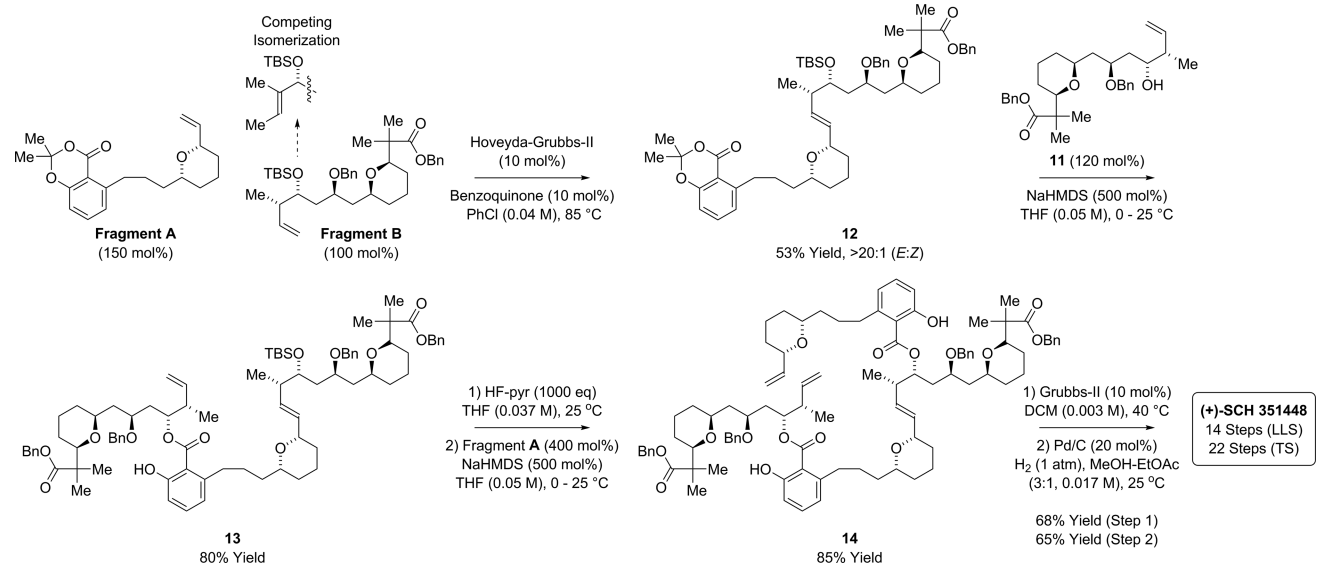
[a]Yields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis. CSA refers to (*S*)-camphorsulfonic acid. Identical yields and diastereoselectivities are observed upon use of recovered (*R*)-IrLn in the conversion of **8** to **9**. See Supporting Information for further details.

ozonolysis delivered aldehyde **10**. Transfer hydrogenative crotylation of **10** provided the homoallylic alcohol **11** with good levels of *anti*-diastereoselectivity (12:1 dr) accompanied by complete levels of stereocontrol at the newly formed carbinol stereocenter. Conversion to the TBS ether completes the synthesis of Fragment **B** in a total of eight steps (LLS). Previously Fragment **B** was prepared in 18 steps (LLS).[12h]

The assembly of Fragments **A** and **B** to form (+)-SCH 351448 is accomplished in a stepwise manner through successive esterification and cross-metathesis reactions (Scheme 4). Initial attempts at the cross-metathesis of Fragments **A** and **B** using conditions reported by Panek[12h] suffered from competing isomerization.[27] Using the second generation Hoveyda–Grubbs catalyst in combination with 1,4-benzoquinone,[28] isomerization is suppressed and the desired product of cross-metathesis **12** is formed in 53% yield. Exposure of compound **12** to the secondary alcohol **11** in the presence of sodium hexamethyldisilazide (NaHMDS) provides the product of transesterification **13** in 80% yield. This transformation was quite sensitive to moisture, and optimal results required use of reactants dried through repeated evaporation from benzene. Removal of the TBS protecting group followed by a second transesterification provides compound **14** in 85% yield. Finally, ring-closing metathesis followed by concomitant hydrogenation and hydrogenolysis of the two olefins, two benzyl ethers, and two benzylic esters (inclusive chemoselection) provides (+)-SCH 351448 in 14 steps (LLS).[29]

In summary, the macrodiolide ionophore (+)-SCH 351448, a type I polyketide bearing 14 stereogenic centers, is prepared in 14 steps (LLS). In eight prior syntheses, 22–32 steps (LLS) were required. An analysis of reaction type across each route suggests enhanced efficiency may be attributed to the use of multiple chemoselective and redox-economic[3] functional group interconversions, a conclusion that adds clarity *vis-à-vis* strategy selection amid an ever-expanding and evolving lexicon of synthetic methods. Future studies will focus on the discovery, development, and application of catalytic methods for protecting-group-free skeletal assembly that merge redox and C–C bond construction events.[3]

Scheme 4. Union of Fragments A and B and Total Synthesis of (+)-SCH 351448[a]



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on selectivity in chemical synthesis, see: (a) Trost, B. M. *Science* **1983**, *219*, 245. (b) Trost, B. M. *Science* **1991**, *254*, 1471. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

(2) For selected reviews on site-selectivity, see: (a) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759. (b) *Site-Selective Catalysis*; Kawabata, T., Ed.; Topics in Current Chemistry; Springer: Cham, Switzerland, 2016; Vol. *372*.

(3) Review: Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(4) "*Given the fact that every* reaction *may be optimized··· the total number of chemical transformations is the only variable in the determination of strategic efficiency. Obviously, the fewer the total number of* reactions *steps in a synthetic design, the higher the level of strategic efficiency.*" Qiu, F. *Can. J. Chem.* **2008**, *86*, 903. In our analysis of prior syntheses, a step is defined as an operation that does not involve any intervening purification/separation, including removal of solvent, commencing with compounds that are over $50/gram

(5) "*The ideal synthesis creates a complex skeleton··· in a sequence only of successive construction* reactions *involving no intermediary functionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality.*" Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784.

(6) For selected reviews that take inventory of transformations used at the process level in the synthesis of advanced pharmaceutical intermediates, see: (a) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Process Res. Dev.* **2005**, *9*, 253. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (c) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443.

(7) A total of 65 steps are required in the commercial manufacturing route to eribulin (Halaven), of which half are devoted to oxidation level adjustments and protecting group manipulations: Yu, M. J.; Zheng, W.; Seletsky, B. M. *Nat. Prod. Rep.* **2013**, *30*, 1158.

(8) For selected reviews on protecting-group-free chemical synthesis, see: (a) Hoffmann, R. W. *Synthesis* **2006**, *2006*, 3531. (b) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193. (c) Saicic, R. N. *Tetrahedron* **2014**, *70*, 8183. (d) Addition/Correction: Saicic, R. N. *Tetrahedron* **2015**, *71*, 2777.

(9) For selected reviews on hydrogenative and transfer hydrogenative C−C coupling, see: (a) Hassan, A.; Krische, M. J. *Org. Process Res. Dev.* **2011**, *15*, 1236. (b) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142. (c) Shin, I.; Krische, M. J. *Top. Curr. Chem.* **2015**, *372*, 85. (d) Feng, J.; Kasun, Z. A.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 5467.

(10) For the isolation of (+)-SCH 351448 and its initial biological evaluation, see: Hegde, V. R.; Puar, M. S.; Dai, P.; Patel, M.; Gullo, V. P.; Das, P. R.; Bond, R. W.; McPhail, A. T. *Tetrahedron Lett.* **2000**, *41*, 1351.

(11) For a review on polyether ionophores, see: Kevin, D. A., II; Meujo, D. A. F.; Hamann, M. T. *Expert Opin. Drug Discovery* **2009**, *4*, 109.

(12) For total syntheses of (+)-SCH 351448, see: (a) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.* **2004**, *126*, 2680. (b) Kang, E. J.; Cho, E. J.; Ji, M. K.; Lee, Y. E.; Shin, D. M.; Choi, S. Y.; Chung, Y. K.; Kim, J.-S.; Kim, H.-J.; Lee, S.-G.; Lah, M. S.; Lee, E. *J. Org. Chem.* **2005**, *70*, 6321. (c) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481. (d) Soltani, O.; De Brabander, J. K. *Org. Lett.* **2005**, *7*, 2791. (e) Bolshakov, S.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 3809. (f) Crimmins, M. T.; Vanier, G. S. *Org. Lett.* **2006**, *8*, 2887. (g) Cheung, L. L.; Marumoto, S.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 3101. (h) Zhu, K.; Panek, J. S. *Org. Lett.* **2011**, *13*, 4652.

(13) For formal syntheses of (+)-SCH 351448, see: (a) Chan, K.-P.; Ling, Y. H.; Loh, T.-P. *Chem. Commun.* **2007**, 939. (b) Park, H.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 3742. (c) Also, see: Backes, J. R.; Koert, U. *Eur. J. Org. Chem.* **2006**, *2006*, 2777.

(14) For a review of the syntheses of (+)-SCH 351448, see: Hiersemann, M. *Nachr. Chem.* **2006**, *54*, 867.

(15) Reviews: (a) Brown, M. S.; Goldstein, J. L. *Science* **1986**, *232*, 34. (b) Brown, M. S.; Goldstein, J. L. *Cell* **1997**, *89*, 331.

(16) For selected reviews of alkene metathesis in natural product total synthesis, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (b) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. (c) Lei, X.; Li, H. *Top. Curr. Chem.* **2012**, *327*, 163.

(17) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (c) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (d) Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350.

(18) Reviews: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(19) For the pyran synthesis *via* sequential nucleophilic and electrophilic allylations, see: Shin, I.; Wang, G.; Krische, M. J. *Chem. - Eur. J.* **2014**, *20*, 13382.

(20) For a review of the *B*-alkyl Suzuki reaction in natural product total synthesis, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(21) (a) Kiyooka, S.-i.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276. (b) Kiyooka, S.-i.; Kaneko, Y.; Kume, K.-i. *Tetrahedron Lett.* **1992**, *33*, 4927.

(22) (a) Fuwa, H.; Noto, K.; Sasaki, M. *Org. Lett.* **2010**, *12*, 1636. (b) Fuwa, H.; Noto, K.; Sasaki, M. *Org. Lett.* **2011**, *13*, 1820. (c) Fuwa, H.; Ichinokawa, N.; Noto, K.; Sasaki, M. *J. Org. Chem.* **2012**, *77*, 2588. (d) Fuwa, H.; Noguchi, T.; Noto, K.; Sasaki, M. *Org. Biomol. Chem.* **2012**, *10*, 8108.

(23) Review: Fuwa, H. *Heterocycles* **2012**, *85*, 1255.

(24) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546.

(25) (a) Cramer, R. *J. Am. Chem. Soc.* **1967**, *89*, 4621. (b) Jesse, A. C.; Cordfunke, E. H. P.; Ouweltjes, W. *Thermochim. Acta* **1979**, *30*, 293.

(26) Sádaba, D.; Delso, I.; Tejero, T.; Merino, P. *Tetrahedron Lett.* **2011**, *52*, 5976.

(27) For a review describing related olefin isomerizations, see: Donohoe, T. J.; O'Riordan, T. J. C.; Rosa, C. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1014.

(28) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

(29) As observed in prior syntheses, direct macrodiolide formation through double transesterification or double cross-metathesis could not be achieved.

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