Published in final edited form as:

J Am Chem Soc. 2016 July 6; 138(26): 8088–8091. doi:10.1021/jacs.6b04917.

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

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Abstract

The polyketide natural product (+)-SCH 351448, a macrodiolide ionophore bearing 14 stereogenic centers, is prepared in 14 steps (LLS). In 8 prior syntheses, 22–32 steps were required. Multiple chemoselective and redox-economic functional group interconversions collectively contribute to a step-change in efficiency.

Graphical Abstract

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-economy³ have the greatest potential to impact step-economy, which may be considered the primary indicator of strategic efficiency⁴ 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.^{6,7,8} Guided by these concepts, we have developed a lexicon of catalytic methods⁹ 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}

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

Here, we sought to deploy multiple chemoselective and redox-economic methods – those developed within and beyond our laboratory – to unambiguously 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 8 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

(+)-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 low density lipoprotein receptor (LDL-R) promoter (IC₅₀ = 25 μ M). 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 hyper-cholesterolemia.^{12–14}

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/RCM reactions.¹⁶ For the synthesis of Fragment **A**, 4 consecutive metal catalyzed reactions are employed: cross-metathesis to form alcohol **2**,^{16,19} tandem nucleophilic^{17a,b} and electrophilic¹⁸ 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 8 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} delivers 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 6 functional groups (2 olefins, 2 benzyl ethers, 2 benzyl esters) – represents a redox event that embodies a high degree of inclusive chemoselectivity. Finally, 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.

The synthesis of Fragment **A** is achieved using 4 consecutive metal catalyzed transformations (Scheme 2). Cross-metathesis of 5-hexen-1-ol **1** with *cis*-1,4-diacetoxy-2-butene¹⁹ 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 late transition metal-olefin π -complex decreases with increasing degree of olefin substitution.²⁵ Tsuji-Trost cyclization¹⁸ converts the homoallylic alcohol **3** to the 2,6-*cis*-disubstituted pyran **4** with complete levels of diastereoselectivity, as determined by ¹H 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 4 steps (LLS).

The synthesis of Fragment **B** begins with Moffatt-Swern oxidation of 5-pentenol **1** (Scheme 3).²⁶ The resulting aldehyde **6** is subjected to Kiyooka's variant of the enantioselective Mukaiyama aldol reaction²¹ 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 ¹H 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 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 8 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 step-wise 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 trans-esterification **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 8 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-economic³ 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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM069445) are acknowledged for partial support of this research.

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

Total ^b or Formal ^c 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 (<i>This Work</i>)	14 (22)	8 (57%)	3 (21.5%)	3 (21.5%)	0

Figure 1.

The 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

^aFor 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.

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

Scheme 2.

Synthesis of Fragment **A** using 4 consecutive metal catalyzed transformations.^a

^aYields 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.

Scheme 3. Synthesis of Fragment **B**.^a

^aYields 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.

Scheme 4. Union of Fragments **A** and **B** and total synthesis of (+)-SCH 351448.^a^aYields are of material isolated by silica gel chromatography. See Supporting Information for further details.