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Search for Highly Efficient, Stereoselective, and Practical Synthesis of Complex Organic Compounds of Medicinal Importance as Exemplified by the Synthesis of the C21–C37 Fragment of Amphotericin B

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As the ability of the synthetic community to assemble a wide variety of highly complex natural products and related compounds of biological and medicinal importance increases, what is becoming increasingly desirable is to develop “ultimately” satisfactory and potentially practical multi-step syntheses. Since linear reaction series of 20, 25, and 30 steps of 90% yield each lead to overall yields of only 12, 7, and 4%, respectively, it would appear desirable to limit the maximum number of steps in the longest linear sequence of any practical synthesis preferably to 20–25 or 30 even in some extreme cases. If the yield of each step is reduced to 80%, the overall yields of 12, 7, and 4% quoted above will be reduced to 1.2, 0.4, and 0.1%, respectively. If one considers the synthesis of amphotericin B (**1**) vis-à-vis the numbers of steps quoted above, it would seem desirable to synthesize the C21–C37 fragment (**2**) in 15 steps or less from readily available starting compounds in a practically desirable combined yield of 20%.

Amphotericin B (**1**), a polyene antibiotic of considerable medicinal significance produced by *Streptomyces nodosus*,^[1] a filamentous bacterium, embodies an architecturally interesting 38-membered macrocyclic skeleton containing eleven oxygenated and four carbon-branched asymmetric carbon centers as well as seven conjugated (*E*)-disubstituted C=C bonds in addition to one carboxylic group and one bridging hemiacetal.^[2,3] Despite many attempts, the total synthesis of amphotericin B (**1**) has been achieved only once by Nicolaou and his coworkers,^[3f] while the group of Masamune^[4] has been the only other group that has reached the aglycone of **1**, i.e., amphoteronolide. The C33–C37 fragment has been successfully synthesized by Masamune,^[4a] McGarvey,^[5] Nicolaou,^[3d] and Kinoshita.^[6] In 2001, the synthesis of a C33–C37 fragment (**3d**) was shortened to 14 steps by Carreira.^[7] Noteworthy, however, is a report in 1982 by Brooks and Kellogg^[8] of the synthesis of a C33–C37 fragment (**3c**) in 9 steps in 17% overall yield, despite a disappointingly low diastereomeric ratio (d.r. hereafter) 2.5/1 in the critical aldol reaction of an enoxyborane.

Herein we report that (i) a highly efficient synthesis of a C32–C37 fragment (**7**) of 98% isomeric purity was achieved from ethyl (*S*)-3-hydroxybutyrate by application of Brown crotylboration^[9] and Fráter-Seebach alkylation,^[10] (ii) highly selective and efficient syntheses of C21–C32 oligoene fragment of amphotericin B through appropriate uses of Horner-Wadsworth-Emmons reaction^[11] (HWE reaction hereafter), alkyne hydrozirconation,^[12] Pd-catalyzed Negishi coupling,^[13] and Heck reaction^[14] were discussed, (iii) the C21–C37 fragment (**2**) of amphotericin B was constructed in a highly

concise and efficient strategy, which exemplify the high competence of delicate design of organic synthesis toward optimized synthesis of complex natural products.

Retrosynthetic analysis of C21–C37 fragment (2) of amphotericin B

As shown in Scheme 1, the C21–C37 fragment of amphotericin B (**2**) can be divided into two smaller fragments, i.e., C33–C37 fragment (**3**) and C21–C32 fragment (**4**), which were used by Masamune^[4d] in a highly convergent way to synthesize C21–C37 fragment of amphotericin B (**2**) through HWE reaction. In this case, C21–C32 fragment (**4**) is an oligoenoic ester which can be, in principle, prepared conveniently through alkyne elementometallation–Negishi alkenylation protocol comprehensively developed in our group.^[15] At the same time, for the construction of **3** from **7**, loss of one carbon atom in oxidative cleavage of alkene by OsO₄/NaIO₄ promoted us to consider an alternative position of dissection at C28–C29 where the precursor **6** and an aldehyde derivable from **5** can be coupled also through HWE reaction.^[11] If the precursor **5** can be directly available through the Heck alkenylation^[14] of the C32–C37 fragment (**7**), while obviating oxidative cleavage of **7**, such route would provide a potentially more direct approach to **2**. For either strategy, a highly selective and efficient synthesis of the C32–C37 fragment (**7**) is desirable.

Negishi–HWE route for the synthesis of the C21–C37 fragment (2) of amphotericin B

Highly efficient preparation of the C32–C37 fragment (7) and the C33–C37 fragment (3) of amphotericin B

A new strategy has been applied for the construction of the C32–C37 fragment (**7**) by employing Fráter-Seebach alkylation^[10] and Brown crotylboration^[9] as key steps. Starting from commercially available ethyl (*S*)-3-hydroxybutyrate, **10** was obtained by Fráter-Seebach alkylation^[10] followed by *in situ* protection of hydroxyl group with TESCl in 80% isolated yield with d.r. of 95/5 (Scheme 2). After reduction of **10** with 1.05 equiv *i*Bu₂AlH, Brown crotylboration^[9] gave intermediate **11** with 95/5 d.r., and its chromatographic purification afforded **11** with 98% isomeric purity in 81% isolated yield. Protection of the new generated hydroxyl group was realized by using TBSOTf in the presence of Hünig's base in DMF. Thus, a highly efficient and stereoselective 4-step synthesis of the C32–C37 fragment (**7**) of 98% isomeric purity was achieved in 52% overall yield from ethyl (*S*)-3-hydroxybutyrate. Oxidative cleavage of **7** led to aldehyde **3** in 87% yield with full retention of stereochemistry established in earlier steps.

A summary of previous syntheses of **3** is shown in Table 1 which indicates substantial improvements accomplished in our synthesis of the crucial intermediate **3**. Earlier syntheses of the C33–C37 fragment by Masamune,^[4d] McGarvey,^[5b] Nicolaou,^[3d] Kinoshita,^[6] and Carreira^[7] generally required 14–20 steps in lower than 30% overall yield. Hanessian's preparation of a C32–C37 fragment reported in 1987^[16] also required 18 steps in only 3% overall yield. Although Brooks' synthesis^[8] of the C33–C37 fragment was realized in only 9 steps in 17% overall yield, but the diastereomeric ratio was only 2.5/1, which severely compromised its practical value. In our current study, starting from ethyl (*S*)-3-hydroxybutyrate, a highly efficient and selective synthesis of the C33–C37 fragment (**3**) of 98% isomeric purity was achieved only in five steps in 46% overall yield.

Stereoselective synthesis of ethyl (all-*E*)-12-hydroxy-dodeca-2,4,6,8,10-pentaenoate (13)

The synthesis of pentaene precursors generally involves repetitive application of HWE olefination. In 1980s, an ingenious 7-step synthesis of 12-phosphododecapentaenoic ester from cyclooctatetraene was developed by Masamune's group^[4] which takes advantage of

the triene moiety of tetraene. In the meantime, we are wondering if the protocol of alkyne hydrozirconation–Negishi alkenylation^[15] could be applied to the synthesis of 12-phosphonododecapentaenoic ester. To avoid multiple use of *in situ* protection of the terminal hydroxyl group with *i*Bu₂AlH or Et₂Zn, TBS-protected propargyl alcohol was used. In the alkyne hydrozirconation–Pd-catalyzed alkenylation protocol, sequential hydrozirconation of TBS-protected (*E*)-2-penten-4-yn-1-ol, Negishi coupling with (*E*)-BrCH=CHC≡CTMS (**9**) in the presence of 1 mol% of PEPPSI,^[17] and removal of the TMS group with K₂CO₃ in methanol gave the trienyne (**12**) of 98% all-*E* geometry in 74% yield. Hydrozirconation of the above obtained trienyne (**12**) with *in situ* generated Schwartz reagent at 23 °C followed by Negishi coupling with ethyl (*E*)-3-bromoacrylate did give the desired pentaene product **13** with 98% isomeric purity, but the yield of this step was only 30%. Evidently, the hydrozirconation of trienyne produced a thermal unstable product, which decomposed quickly at 23 °C. The yield of this step was improved to 60% by using freshly prepared Schwartz reagent to perform hydrozirconation at 0 °C followed by Negishi coupling with ethyl (*E*)-3-bromoacrylate in the presence of 5 mol% of PEPPSI. After removal of the TBS-protecting group by TBAF, **13** was obtained in 28% overall yield in 7 longest linear steps from propargyl alcohol.

Coupling of aldehyde **3** with **13** for the synthesis of the C21–C37 fragment by HWE reaction

According to Masamune's procedure,^[4d] bromination and phosphonation of **13** followed by HWE olefination with **3** gave the C21–C37 fragment (**2**) of amphotericin B in 40% yield in three steps. The longest linear steps of this route were 10 steps and the overall yield is 11% with 98% isomeric purity.

Negishi–Heck–HWE route to the C21–C37 fragment (**2**) of amphotericin B

Highly efficient and stereoselective synthesis of diethoxyphosphorylated trienoate (**6**)

The common pathway toward diethylphosphorylated trienoate is bromination and phosphonation of the corresponding unsaturated alcohols, such as ethyl (2*E*,4*E*,6*E*)-8-hydroxy-octa-2,4,6-trienoate (**14**). The alkyne elementometallation–Pd-catalyzed cross-coupling sequential processes have been comprehensively developed for selective syntheses of alkenes, dienes, oligoenes, and oligoenynes.^[15,18] As summarized in Scheme 4, **6** was synthesized by employing our recently developed procedure involving alkyne hydrozirconation–Negishi alkenylation strategy.^[19] Hydrozirconation of *in situ* metalated propargyl alcohol by using *in situ* generated Schwartz reagent^[20] followed by iodinolysis gave (*E*)-3-iodo-3-propen-1-ol. After *in situ* metalation with Et₂Zn, Negishi alkenylation with diethynyl zinc in the presence of 1 mol% of Pd(DPEphos)Cl₂ afforded (*E*)-pent-2-en-4-yn-1-ol (**8**) in 62% overall yield in two steps from propargyl alcohol. Hydrozirconation of metalated enyne and Negishi alkenylation with ethyl (*E*)-3-bromoacrylate in the presence of 1 mol% of PEPPSI gave the desired ethyl (2*E*,4*E*,6*E*)-8-hydroxy-octa-2,4,6-trienoate (**14**) in 79% isolated yield. After bromination and phosphonation, trienoic synthons (**6**) of 98% isomeric purity was obtained in 40% yield in 5 steps from propargyl alcohol.

Synthesis of the C21–C37 fragment (**2**) by using Negishi–Heck–HWE route

With **7** in hand, palladium-catalyzed Heck alkenylation of **7** with (*E*)-BrCH=CHCO₂Et was investigated. Jeffery's conditions^[21] in the presence of 10 mol% of Pd(OAc)₂ and 1.2 equiv of AgOAc in DMF was found to be effective in converting **7** into 98% isomerically pure **5** in 74% yield (38% in 5 steps from ethyl (*S*)-3-hydroxybutyrate). After its sequential reduction with *i*Bu₂AlH and oxidation with MnO₂, HWE olefination with ethyl (2*E*,4*E*,6*E*)-8-(diethoxyphosphoryl)octa-2,4,6-trienoate (**6**) in the presence of LiN(SiMe₃)₂ afforded

the desired the C21–C37 fragment (**2**) of >98% isomeric purity in 77% isolated yield. The overall yield was 25% in 8 longest linear steps from ethyl (*S*)-3-hydroxybutyrate.

In summary, the synthesis of the C21–C37 fragment (**2**) of amphotericin B has been designed and investigated as a model for efficient, stereoselective, and practical synthesis of oligoenes and oligoenynes, representing a large number of important natural products. Of the two synthetic strategies we have investigated, the Negishi–Heck–HWE route proved superior to Negishi–HWE route by virtue of both higher overall yield (25% vs. 11%) and shorter longest linear sequence (8 vs. 10 steps). This study has demonstrated various synthetically superior features in terms of product yields, efficiency, and stereo- as well as regioselectivities associated with the alkyne hydrometalation–Pd-catalyzed Negishi coupling routes to conjugated oligoenes. At the same time, however, this study has also shown the desirability of consideration of all available synthetic options for finding the ultimately optimized and satisfactory synthetic route to a given target, as exemplified in the synthesis of the C21–C37 fragment (**2**) of amphotericin B.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Synthetic strategies for the synthesis of the C21-C37 fragment (2) of amphotericin B.

Scheme 2.

Synthesis of the C32–C37 fragment (**7**) and the C33–C37 fragment (**3**).

Scheme 3.

Synthesis of the C21–C37 fragment (**2**) by using Negishi–HWE protocol.

Scheme 4.

Highly efficient and stereoselective synthesis of diethoxyphosphorylated trienoate (**6**).

Scheme 5.

Highly efficient synthesis of the C21-C37 fragment (**2**) by using Negishi-Heck-HWE route.

Table 1

Comparison of previous syntheses of the C33–C37 (or C32–C37) fragments of amphotericin B.

Structure	R ¹	R ²	Major author (published year)	No. of steps	Overall yield (%)	Starting compound	ref
3	TBS	TES	current work	5	46	Ethyl (S)-3- hydroxybutyrate	
3	TBS	TES	Masamune (1985)	15	29	Roche ester	4d
3a	TBS	THP	Nicolaou (1988)	20	27	(EtO ₂ CCHOH) ₂	3d
3b	TBS	MEM	McGarvey (1986)	18	7	aspartic acid	5b
3c	PhCO	TBS	Brooks (1982)	9	17 dr = 2.5/1	EtO ₂ CCH ₂ CH (OH)Me	8
3d	TES	TIPS	Carreira (2001)	14	16	tiglic aldehyde	7
3e			Hanessian (1987)	18	3	(S)-glutamic acid	16

TBS: *tert*-butyl dimethyl silyl. TES: triethylsilyl. MEM: β -methoxyethoxymethyl. MOM: methoxymethyl. TIPS: triisopropylsilyl. Tr: triphenylmethyl.