Pure Appl. Chem., Vol. 77, No. 12, pp. 2073–2081, 2005.
DOI: 10.1351/pac200577122073

Oxacycle synthesis via radical cyclization of β-alkoxyacrylates*

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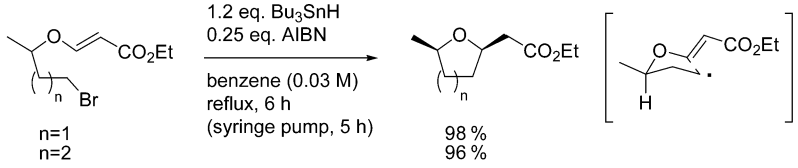
Abstract: Oxolane and oxane units in oxacyclic natural products were prepared via radical cyclization reaction of β-alkoxyacrylates, β-alkoxymethacrylates, and β-alkoxyvinyl ketones.

Keywords: β-Alkoxyacrylates; ambruticin; pamamycin-607; lasonolide A; SCH 351448; radical cyclization.

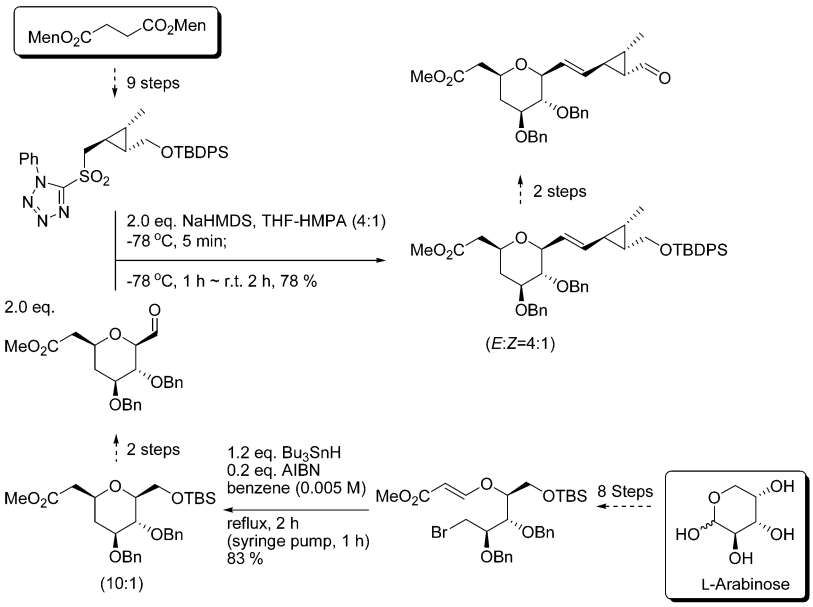
Radical cyclization reaction of β-alkoxyacrylates is now well known to produce *cis*-2,5-disubstituted oxolanes and *cis*-2,6-disubstituted oxanes stereoselectively [1] (Scheme 1). The stereoselectivity is a manifestation of heteroatom effect in that *s-trans* conformation of the oxygen-β-carbon bond is more favored in the Stork–Beckwith transition state. It may be compared with a lower *cis*-selectivity (<3:1) in the related carbacycle synthesis [2] and leads to a new avenue in the synthesis of oxacyclic natural products.



Scheme 1 Radical cyclization of β-alkoxyacrylates.

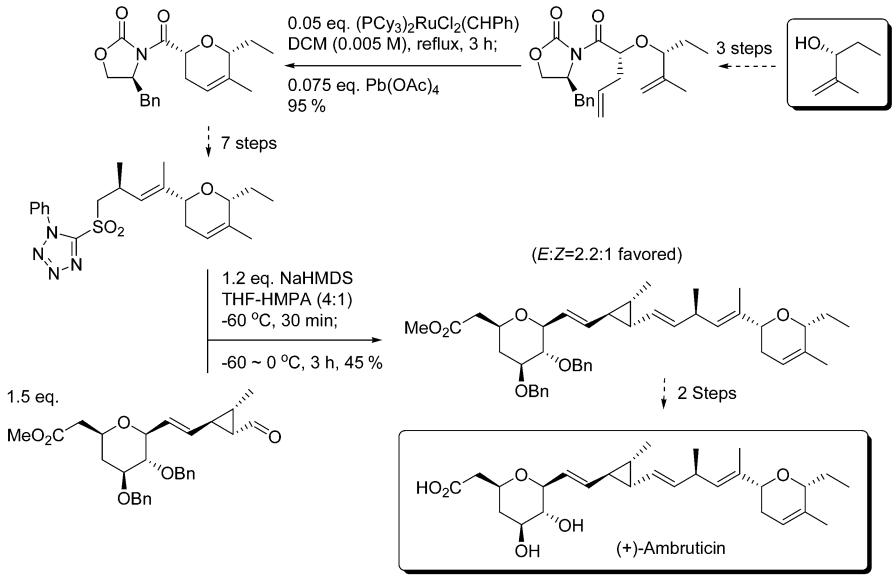
Ambruticin is an orally active antifungal agent isolated from fermentation extracts of the Myxobacteria species *Polyangium cellulosum*. It features unique *cis*-2,6-disubstituted oxane and oxene ring systems. In the total synthesis of ambruticin [3], the oxane fragment was prepared via radical cyclization of a β-alkoxyacrylate obtained from L-arabinose (Scheme 2). It was concluded that radical cyclization of β-alkoxyacrylates may be carried out stereoselectively in the presence of extra substituents.

*Paper based on a presentation at the 7th IUPAC International Conference on Heteroatom Chemistry (ICHAC-7), Shanghai, China, 21–25 August 2004. Other presentations are published in this issue, pp. 1985–2132.



Scheme 2 Synthesis of the ring A fragment of ambruticin.

β-Alkoxyacrylate radical cyclization reaction using alkenyl radical species worked in the synthesis of the oxene fragment, but the olefin metathesis protocol offered practical advantage. The two fragments were coupled by Kocienski–Julia reaction for synthesis of ambruticin (Scheme 3).

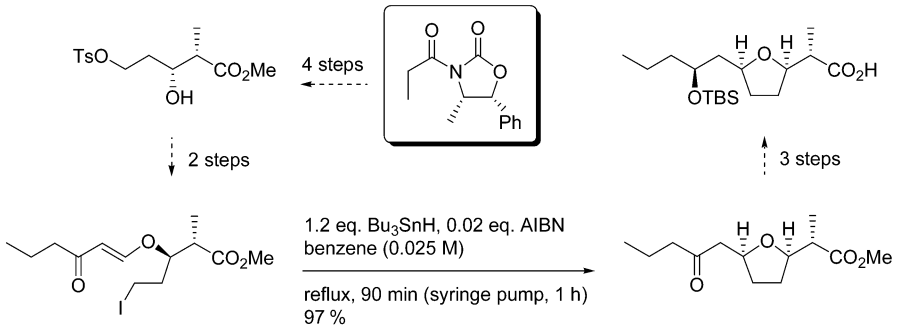


Scheme 3 Preparation of the ring B fragment and completion of the synthesis of ambruticin.

Isolated from *Streptomyces alboniger*, pamamycin-607 is known for its potent activity against gram-positive bacteria including multiple antibiotic-resistant strains of *Mycobacterium tuberculosis* as well as against phytopathogenic fungi. It is a 16-membered macrodiolide incorporating two of the three *cis*-2,5-disubstituted oxolane rings within the macrocycle framework. The most characteristic structural

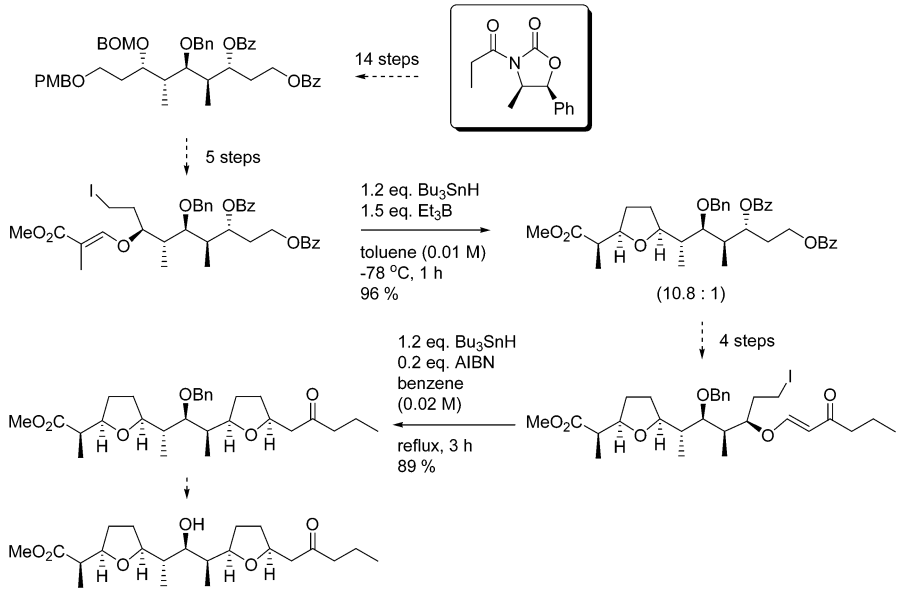
features in pamamycin-607 are *cis*-2,5-disubstituted oxolane rings adjacent to methyl-substituted stereogenic centers. Efficient and stereoselective construction of these structural units is not trivial, and radical cyclization route offers a new breakthrough in this area.

For total synthesis of pamamycin-607 [4], the *erythro-cis* 2-(oxolane)propanoate unit in the southern half was prepared by radical cyclization of a β-alkoxyacrylate precursor obtained via asymmetric aldol reaction (Scheme 4).

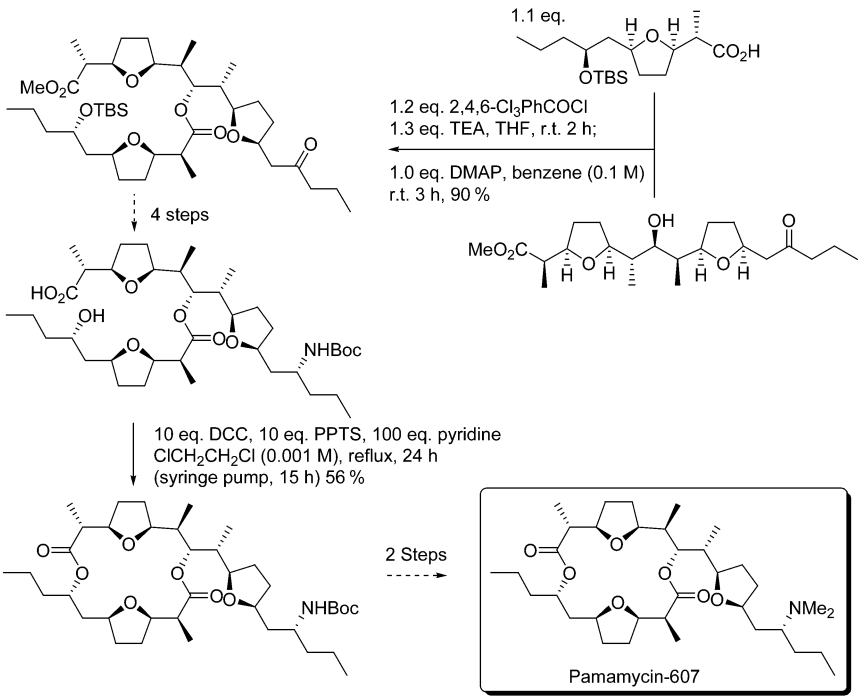


Scheme 4 Preparation of the southern half of pamamycin-607.

Synthesis of the more complex northern half featured radical cyclization of a β-alkoxymethacrylate precursor, which led to a high *threo-cis* selectivity in the 2-(oxolane)propanoate product. In the radical cyclization of β-alkoxymethacrylates, preference for "outside alkoxy" conformation of the intermediate radical species should minimize both allylic 1,3-strain and electrostatic repulsions, and an early transition state for hydrogen abstraction in which attack occurs from the least hindered face of the radical is apparently operative, leading to *threo* products. The third oxolane unit was prepared by radical cyclization of a β-alkoxyvinyl ketone intermediate (Scheme 5). Two separate esterification reactions were carried out to construct the macrodiolide structure of pamamycin-607 (Scheme 6).



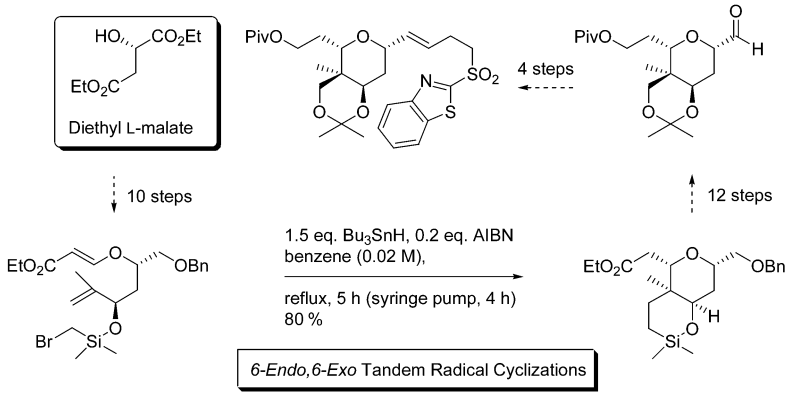
Scheme 5 Synthesis of the northern half of pamamycin-607.



Scheme 6 Total synthesis of pamamycin-607.

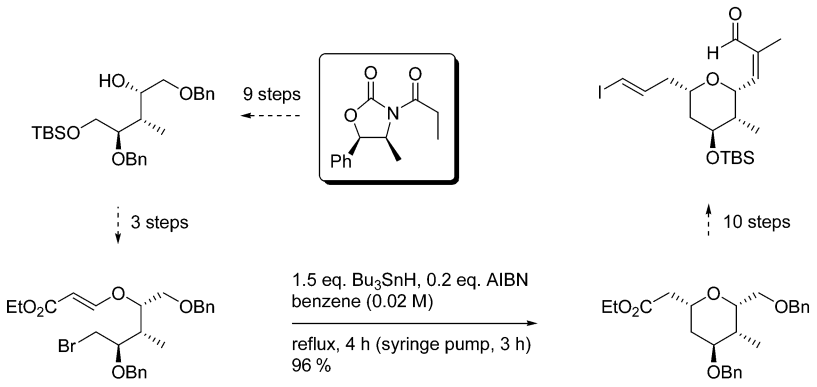
Lasonolide A is a novel cytotoxic macrolide isolated from the shallow water Caribbean marine sponge, *Forcepia* sp. It is a potent cytotoxin against a number of tumor cell lines and a cell adhesion inhibitor. The most characteristic features are the two *cis*-2,6-substituted oxane rings integrated in the macrolide structure. In particular, ring A contains a quaternary stereogenic center at C22 with a methyl and a hydroxymethyl substituent, and a successful synthesis of lasonolide A calls for stereoselective assembly of a *cis*-2,6-substituted oxane unit with the attendant quaternary center.

In the total synthesis of lasonolide A [5], the correct stereochemistry at the quaternary center of the ring A was set up in conjunction with the construction of the *cis*-2,6-disubstituted oxane fragment via a stereoselective tandem radical cyclization of a β-alkoxyacrylate containing bromomethylsilyloxy substituent (Scheme 7).



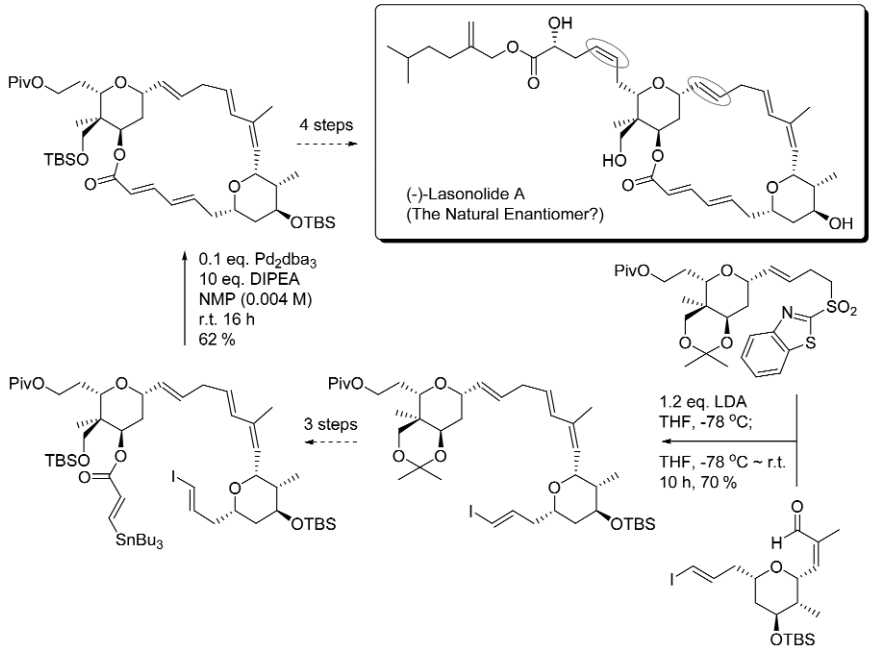
Scheme 7 Preparation of the ring A fragment of lasonolide A.

The ring B fragment was obtained by employing radical cyclization reaction of a β-alkoxyacrylate precursor prepared from asymmetric aldol reaction (Scheme 8). Presence of extra substituents did not interfere with the stereoselective radical cyclization.



Scheme 8 Preparation of the ring B fragment of lasonolide A.

The two fragments were coupled by Julia reaction, and Stille reaction was employed for macrolide ring closure. The original structure proposed and specific rotation value were in error, the correct structure was verified by total synthesis (Scheme 9).

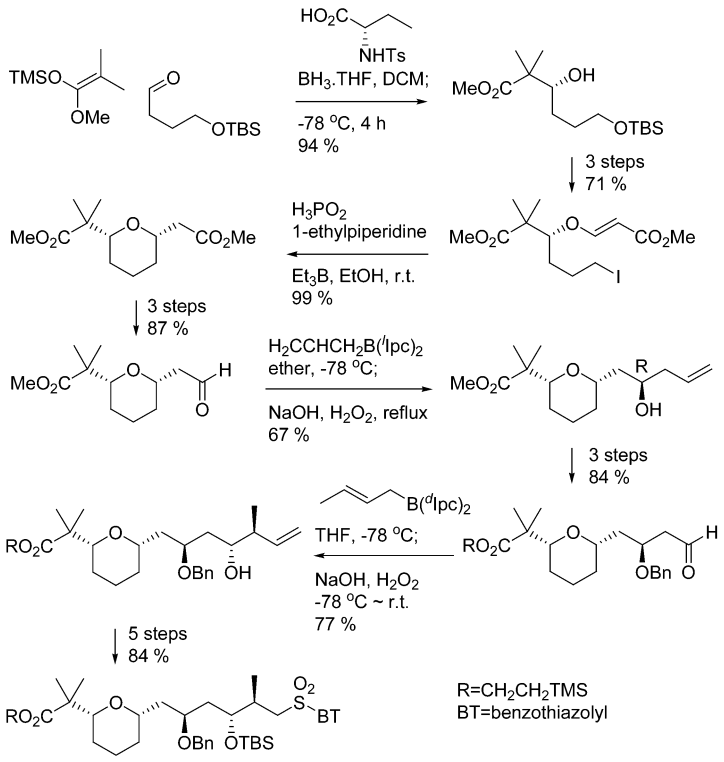


Scheme 9 Total synthesis of lasonolide A.

SCH 351448 was identified from the fermentation broths of a microorganism belonging to *Micromonospora* sp., and it is the first small molecule activator of the LDL-R promoter identified to date. LDL uptake by the LDL receptor (LDL-R) is an important mechanism for clearing serum cholesterol, and selective activators of LDL-R transcription may be able to decrease serum LDL levels by

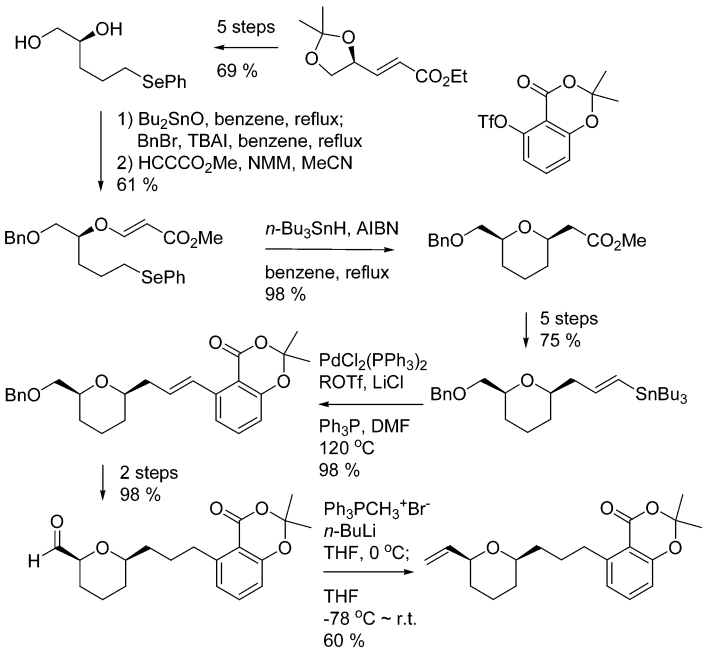
increasing LDL uptake by the LDL-R. The structure of SCH 351448 features a 28-membered macrodiolide consisting of two units of a hydroxy carboxylic acid unit, which possesses two *cis*-2,6-disubstituted oxane rings.

Total synthesis of SCH 351448 required preparation of the ring A and B fragments [6]. Radical cyclization reaction of a β-alkoxyacrylate prepared from asymmetric Mukaiyama aldol reaction led to a diester, which was further elaborated into the ring A fragment via Brown allylation, transesterification, and Brown crotylation (Scheme 10).



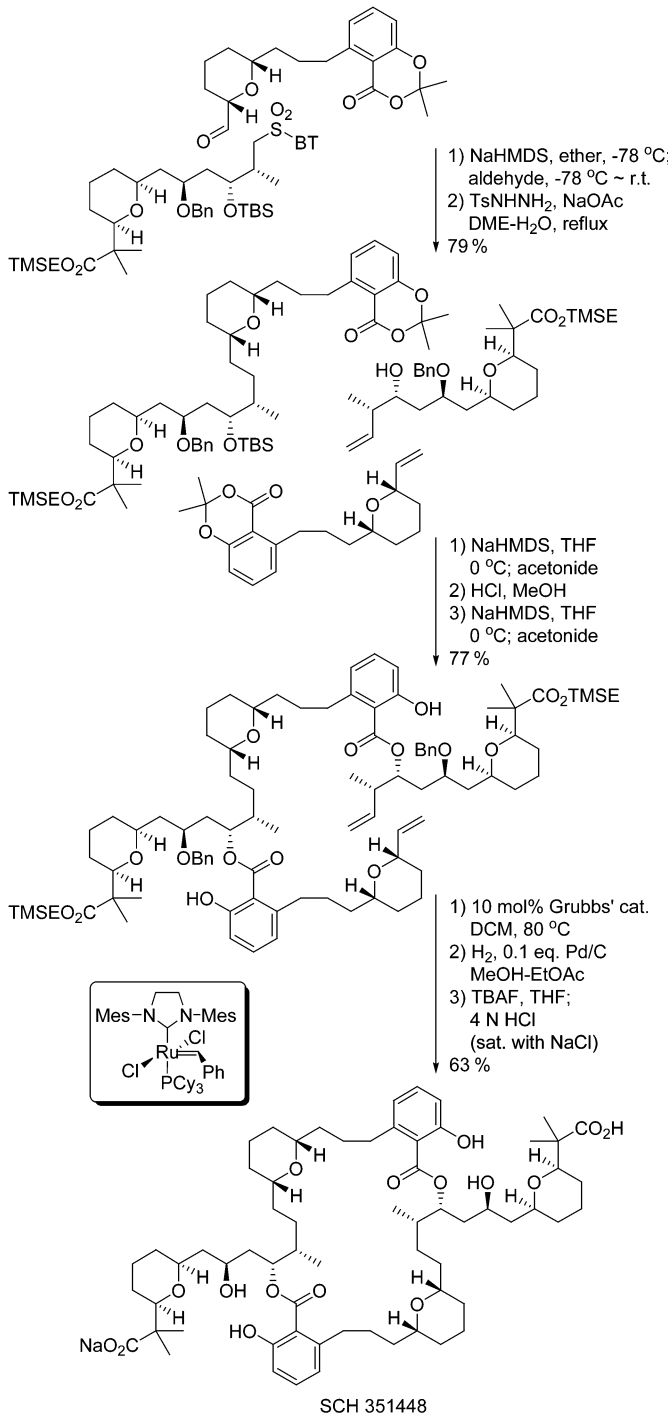
Scheme 10 Preparation of the ring A fragments of SCH 351448.

Preparation of the ring B fragment employed radical cyclization reaction of a β-alkoxyacrylate selenide prepared from glyceraldehyde acetonide. The homologous vinylstannane reacted with salicylate moiety via intermolecular Stille reaction, and subsequent Wittig reaction led to the ring B fragment (Scheme 11).



Scheme 11 Preparation of the ring B fragment of SCH 351448.

The ring A fragment sulfone and the ring B fragment aldehyde were coupled via Julia reaction. The monomer acetonide thus obtained was further transformed into a linear diene diester via sequential alkoxide openings of the salicylic acetonide functionalities. Intramolecular olefin metathesis mediated by the second-generation Grubbs catalyst proceeded smoothly, and the macrodiolide was obtained after hydrogenation–hydrogenolysis. (TMS)ethyl ester functionalities were removed by reaction with TBAF, and the monosodium salt SCH 351448 was obtained when the reaction mixture was equilibrated with 4 N hydrochloric acid saturated with sodium chloride (Scheme 12).



Scheme 12 Total synthesis of SCH 351448.

In conclusion, β-alkoxyacrylate radical cyclization and related reactions offer stereoselective and expeditious routes in the syntheses of complex natural products containing oxolane and oxane rings.

ACKNOWLEDGMENTS

The author thanks coworkers cited in the references, and the Ministry of Science and Technology (Republic of Korea) and KISTEP for a National Research Laboratory grant.

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