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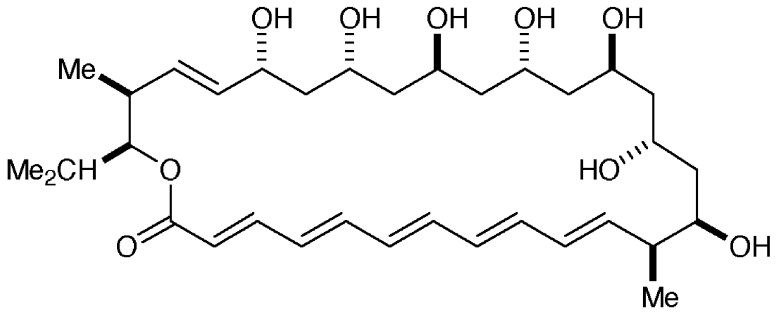

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Synthesis of the Antifungal Macrolide Antibiotic (+)-Roxaticin

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Abstract: The total synthesis of the antifungal macrolide antibiotic roxaticin has been accomplished. The synthesis relies principally on aldol and directed reduction steps to construct the extended 1,3-polyol array present in the natural product. Three principal nonpolyene containing fragments were assembled and then coupled using Julia olefination and methyl ketone aldol addition reactions. A series of functionalization reactions incorporated the sensitive polyene and provided the protected roxaticin seco-acid, which was lactonized in good yield. Acidic deprotection completed this convergent synthesis of roxaticin.

Introduction

Polyene macrolide antibiotics are an important class of natural products currently used in the treatment of systemic fungal infections. Although there are over 200 known members of this family, most of which are produced by soil actinomycetes belonging to the genus *Streptomyces*, only about a dozen representatives have been fully characterized. The unique stereochemical and structural characteristics of these natural products, along with the increasing incidence and severity of acute fungal infections, have stimulated the interest of organic chemists.[1−3] A variety of methods have been developed to independently address the synthesis of both the polyol and polyene portions of these potent fungicides. The first approach to any member of this class was Nicolaou's relay synthesis of amphotericin B in 1988.[4] At that time, amphotericin B was the only polyene macrolide whose structure had been unequivocally established. The strategies and methodologies developed by other groups over the past decade have resulted in the successful total syntheses of five other polyene macrolide antibiotics: mycoticin A,[5] roxaticin (**1**),[6,7] filipin III,[8] roflamycoin,[9] and dermostatin.[10]

Structure. Roxaticin is a pentaene macrolide isolated from streptomycete X-14994, found in the soil near Escalante, Utah, USA.[11] The structure and relative stereochemistry of roxaticin were established by X-ray analysis of the derived heptaacetate (Figure 1). The absolute stereochemistry was proposed on the basis of the observed optical rotation of the $C_{28}-C_{30}$ degradation product, 2,4-dimethyl-1,3-pentanediol, obtained by treatment of the natural product with ozone followed by H_2-Pd/C and sodium borohydride. As is often the case with polyene macrolides, roxaticin exhibits antifungal but not antibacterial activity.

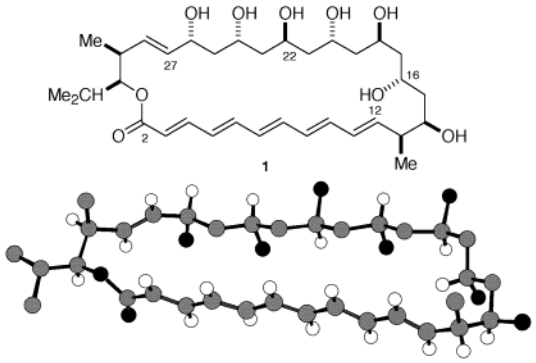

Figure 1. Roxaticin heptaacetate X-ray structure (acetates omitted for clarity).

Our interest in the synthesis of roxaticin was motivated by the fact that the strict polyacetate origin of the roxaticin offered an ideal forum for the extension of our aldol-based approach to polypropionate natural product synthesis. In this paper, we report a highly convergent total synthesis of the naturally occurring (+)-enantiomer of roxaticin, which relies heavily on recent advances in aldol methodologies developed in this laboratory.

Synthesis Plan. Our synthesis plan relied upon the three stereoselective aldol bond constructions illustrated in Scheme 1 (eqs 1−3).[12,13] These transformations provide rapid access to chiral β-hydroxy ketones and ultimately 1,3-dioxygen relationships, the prevalent stereochemical motif found in these natural

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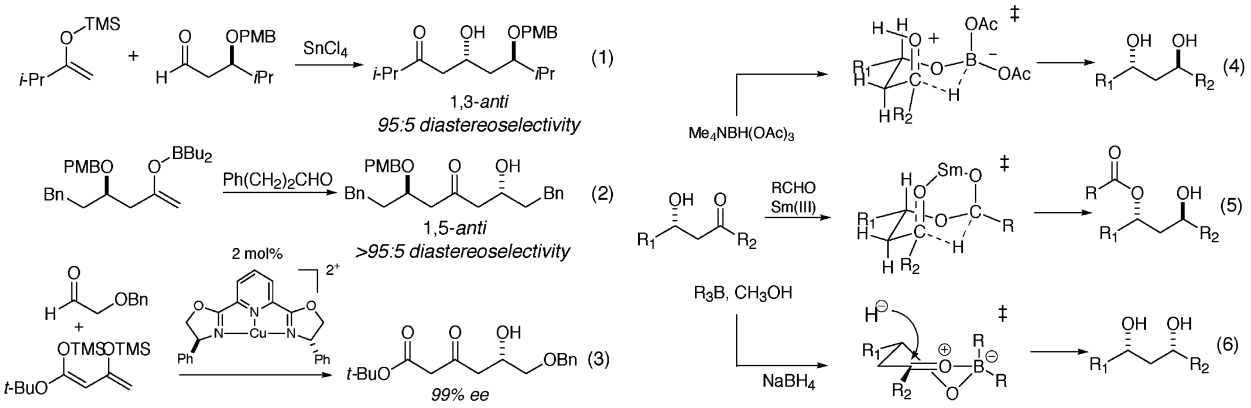
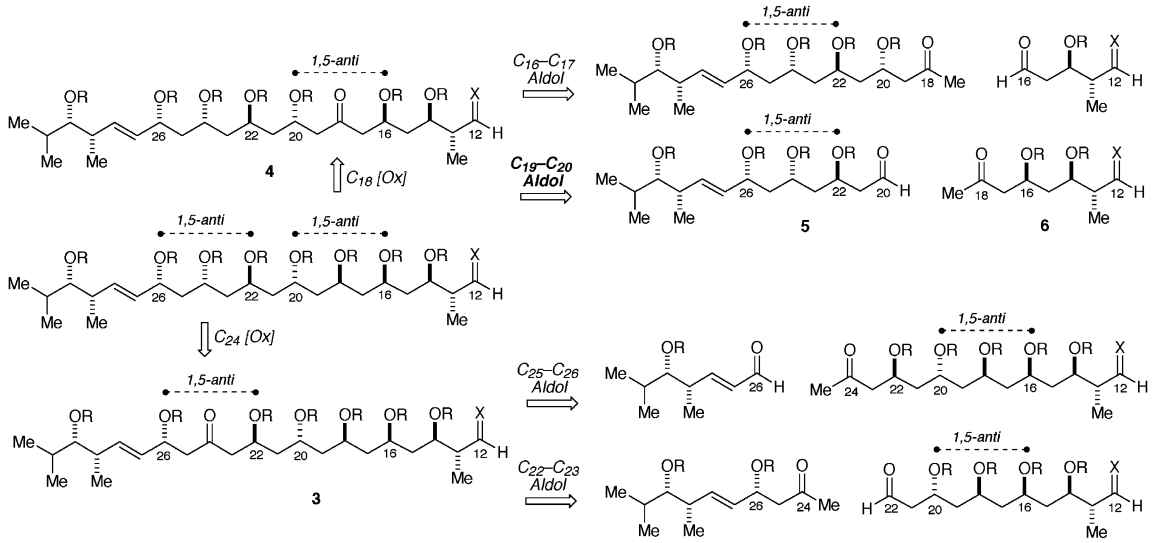
Scheme 1



Scheme 2



product targets. Stereochemical control in these aldol reactions may be derived from the addition of enol nucleophiles to β-alkoxyaldehydes (eq 1)[14] or from remote stereocenters on the enolate coupling partner (eq 2). The remarkable 1,5-anti induction observed in this reaction independently by us[15] and Paterson[16] is particularly well suited to polylene macrolide applications. Silylketene acetal additions to benzyloxyacetaldehyde in the presence of a chiral Cu(II) catalyst provide β-hydroxyketones with excellent enantioselectivity (eq 3).[17] Stereoselective hydride reductions of these nonracemic β-hydroxyketones would provide access to either syn or anti 1,3-diol subunits. We have developed two different methods for the diastereoselective internally directed reduction of β-hydroxyketones, as shown in eqs 4 and 5.[18,19] The highly syn-selective hydride reduction popularized by Prasad[20] (eq 6) allows access to syn diol subunits. With the proper choice of aldol reaction conditions and hydride reduction reagents, any diol subunit can be constructed with control over both relative and absolute stereochemistry.

With these reactions in mind, our synthesis plan for roxaticin (**1**) is outlined in Scheme 2. Given the sensitivity of the pentaene moiety to light and air, this fragment would be incorporated into the fully functionalized polyacetate precursor at a late stage of the synthesis, potentially via a Horner−Wadsworth−Emmons coupling with a C_{12} polyol-derived aldehyde. With this requirement in mind, we find a convergent synthesis relies upon a penultimate seco-acid cyclization[21−23] onto the hindered C_{30} oxygen. The $C_{12}-C_{30}$ fragment contains all the stereocenters present in the natural product, and its synthesis may be considered as the major subgoal of this project.

The 1,5-syn dioxygen relationship displayed on the polyacetate backbone provides the retron for the aldol reaction illustrated in eq 2. The identification of the two such pairwise relationships in the $C_{12}-C_{30}$ synthon is highlighted in Scheme 2, as are the two obligatory ketonic precursors **3** and **4**. Each of these intermediates may be derived from either of two potential

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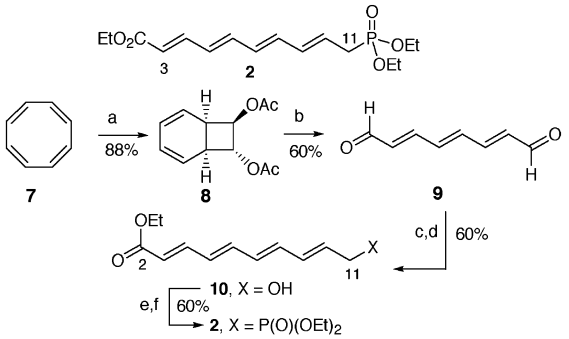
Scheme 3 [a]



[a] Key: (a) $Hg(OAc)_2$, AcOH, Δ; (b) $LiAlH_4$, THF, 0 °C to rt, then O_2; (c) triethylphosphonoacetate, NaH, −78 °C to rt, THF; (d) $NaBH_4$, EtOH; (e) $SOBr_2$, 2,6-di-*tert*-butylpyridine, −20 °C, THF; (f) $(EtO)_3P$, toluene, 110 °C.

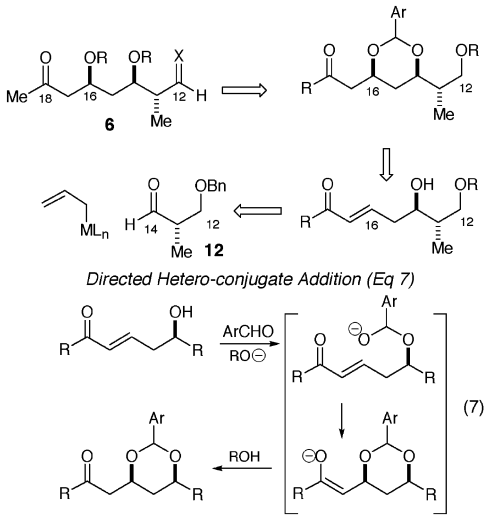
aldol reactions, depending upon which fragments serve as the nucleophilic and electrophilic reaction components. This family of disconnections provides several options for construction of this fragment. The aldol option that was selected was based on the $C_{19}-C_{20}$ aldol bond construction from the two fragments **5** and **6** of most similar complexity. In principle, stereochemical control of this proposed aldol reaction could also arise from a Lewis acid-mediated 1,3-syn aldol union of **5** with the enolsilane of ketone **6** (eq 1), providing additional flexibility to the synthetic plan.

Results and Discussion

C_2-C_{11} Polyene Subunit. Much effort has been devoted to the stereocontrolled synthesis of polyenes.[24,25] They are present not only in antifungal macrolides but also in anticancer retinoids, and they are increasingly being used to explore the concept of molecular electronics. We preferred, for reasons of efficiency and convergency, to incorporate this fragment into the polyol chain in a single stereocontrolled step, rather than to build up the pentaene in a repetitive, stepwise manner. This plan required a practical synthesis of a pentaene fragment coupling precursor. We decided to use methodology developed by Anet[26] to construct a suitable polyene precursor, due to the relative ease with which this segment may be stereoselectively constructed from readily available starting materials. The polyene fragment required would be a phosphonate such as **2**, which would be coupled to polyol C_{12} aldehyde **3** in a trans-selective Horner−Emmons reaction. The synthesis of phosphonate **2** began with commerically available cyclooctatetraene (**7**) (Scheme 3).

As initially reported by Cope, a one-pot electrocyclic ring closure and Hg(II)-catalyzed trans-acetoxyation delivered compound **8** in 88% yield (Scheme 3).[27] Reductive removal of the acetates using $LiAlH_4$, followed by stirring an ethyl acetate solution of the transient diol in air led to 2-electron oxidative ring fragmentation and olefin isomerization to afford the highly unstable dialdehyde **9** in 60% yield. Since **9** was highly sensitive to both air and light and was prone to spontaneous polymerization, it was immediately treated with 1 equiv of the sodium salt of triethylphosphonoacetate to deliver a monoester−monoaldehyde. All subsequent reactions and manipulations of compounds containing this polyene structure were carried out with careful exclusion of light to maximize product yield and stability. Treatment of the unpurified reaction mixture with an excess of sodium borohydride resulted in formation of alcohol **10**, which could be quickly purified by flash chromatography and isolated in 60% yield. Exposure to thionyl bromide at −20 °C provided the corresponding allylic bromide. When this unpurified bromide was heated to reflux in toluene containing an excess of triethyl phosphite, the desired phosphonate **11** was obtained in 60% yield over the two steps. Fortunately, this polyene was the most stable of any intermediate in this sequence and typically could be stored frozen in argon saturated benzene at −20 °C for several months with less than 20% decomposition. Flash chromatography purification was employed to purify this phosphonate immediately before its use (vide infra).

Scheme 4



$C_{12}-C_{19}$ Subunit. The plan for the synthesis of methyl ketone fragment **6** (Scheme 4) evolved from a chelate-controlled allylmetal addition to the readily available β-alkoxy aldehyde **12**, a subsequent homologation, and a stereocontrolled, hemiacetal-mediated heteroconjugate addition (eq 7) to introduce the C_{16}-syn oxygen heteroatom through methodology previously reported by us.[28]

Synthesis of methyl ketone fragment **6** began with aldehyde **12** (Scheme 5). While this aldehyde is available by several routes,[29] we choose to produce it in quantity by asymmetric alkylation of the titanium enolate derived from propionyl oxazolidinone **13** with BOM-Cl[30] followed by reductive removal ($LiBH_4$) of the chiral auxiliary and Parikh−Doering oxidation to the aldehyde. This procedure affords large quantities of enantiopure aldehyde **12** in 85% yield for the three steps. Chelate-controlled allylation ($SnCl_4$, $CH_2{=}CHCH_2SnBu_3$, CH_2Cl_2, −78 °C) by the method of Keck delivered the homoallylic alcohol **14** in 90% yield and 35:1 diastereoselectivity.[31] Temporary protection of the alcohol as its TES ether (99%) was required to efficiently execute the following homologation.

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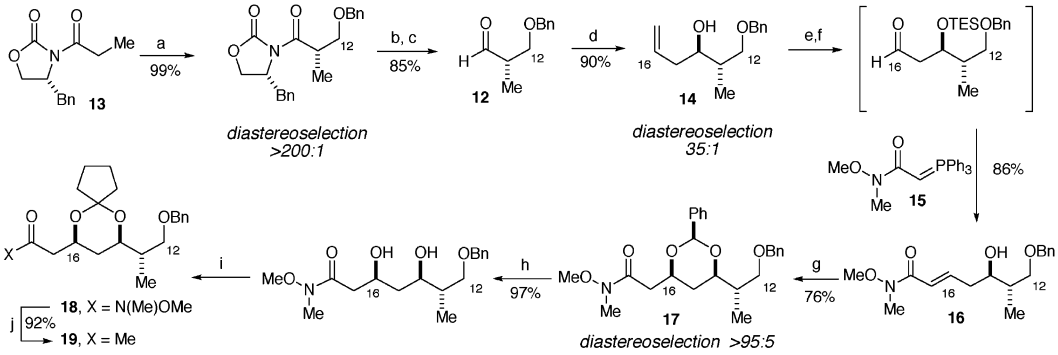
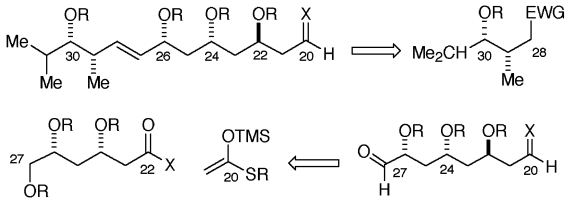
Scheme 5 [a]



[a] Key: (a) $TiCl_4$, NEt_3, $BnOCH_2Cl$, 0 °C, CH_2Cl_2; (b) $LiBH_4$, 0 °C, THF; (c) SO_3·pyr, DMSO, −10 °C, CH_2Cl_2; (d) allyltributyltin, $SnCl_4$, −78 °C, CH_2Cl_2; (e) TESCl, imidazole, CH_2Cl_2; (f) O_3; Ph_3P; then **15**; TsOH, CH_2Cl_2; (g) cat. KHMDS, PhCHO, THF, 0 °C; (h) $Zn(OTf)_2$, EtSH, $NaHCO_3$, CH_2Cl_2; (i) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (j) MeLi, THF, −78 °C.

Scheme 6

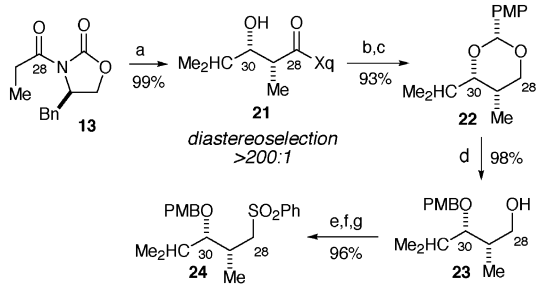


Ozonolysis followed by in situ reduction (Ph_3P) and treatment with *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (**15**)[32] afforded, after acidic workup, amide **16** in 86% yield. Failure to protect alcohol **14** during this reaction resulted in retro-aldol cleavage of the intermediate β-hydroxy aldehyde under the reaction conditions. Amide **16** was induced to undergo intramolecular hemiacetal conjugate addition with catalytic quantities of potassium hexamethyldisilazide (KHMDS) in the presence of excess benzaldehyde (eq 7) to give the thermodynamically favored syn-protected acetal **17** (76%) along with 15% recovered **16**. Since the benzylidene acetal proved to be incompatible with later reductive reaction conditions (vide infra), it was replaced with a cyclopentylidene ketal by treatment with bicarbonate buffered $Zn(OTf)_2$ and EtSH in CH_2Cl_2 followed by acid-catalyzed reprotection to afford amide **18** in 97% yield over the two steps. Finally, treatment of amide **18** with methyllithium at −78 °C gave the desired $C_{12}-C_{19}$ subunit **19** in 92% yield.[33]

$C_{20}-C_{30}$ Subunit. The assembly of this fragment is outlined below (Scheme 6). The trans-selective Julia−Lythgoe coupling[34−36] of the $C_{28}-C_{30}$ propionate subunit to the extended $C_{20}-C_{28}$ polyacetate fragment, the catalytic asymmetric synthesis of the $C_{22}-C_{27}$ fragment and its acetate extension highlight the important bond constructions in the assemblage of this fragment.

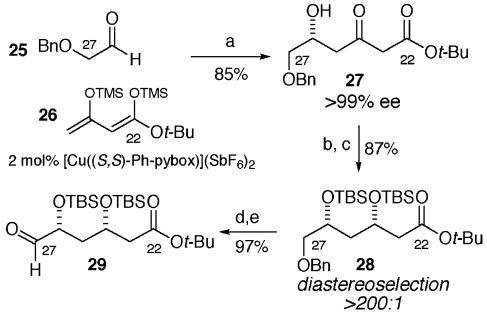
The synthesis was initiated with a boron-mediated aldol reaction of the (*R*)-*N*-propionyl imide **13** with isobutyraldehyde to afford adduct **21** in 99% yield and >200:1 diastereoselectivity (Scheme 7).[37] Reductive removal of the auxiliary with lithium borohydride[38] and direct acetalization with *p*-anisaldehyde

Scheme 7 [a]



[a] Key: (a) Bu_2BOTf, NEt_3, *i*-PrCHO, CH_2Cl_2, −78 °C; (b) $LiBH_4$, MeOH, THF, −78 °C; (c) cat. TsOH, *p*-MeOPhCH(OMe)$_2$, CH_2Cl_2; (d) DIBAl−H, CH_2Cl_2, −78 °C; (e) MsCl, NEt_3, CH_2Cl_2; (f) PhSLi, THF, −78 °C → 23 °C; (g) *m*-CPBA, CH_2Cl_2.

Scheme 8 [a]



[a] Key: (a) ref 17; (b) Et_2BOMe, $NaBH_4$, MeOH, THF, −78 °C; (c) TBSCl, imidazole, CH_2Cl_2; (d) 2000 psi H_2, 10% Pd/C, EtOAc; (e) Dess−Martin, CH_2Cl_2.

dimethylacetal delivered 93% of the protected diol **22**, along with 99% of recovered oxazolidinone. The mixture of **22** and oxazolidinone could be efficiently separated by trituration with hexanes, filtration to collect the crystallized oxazolidinone, and flash chromatography of the mother liquor to deliver pure **23**. Regioselective reductive acetal cleavage at the less-hindered oxygen with DIBAl-H at 0 °C afforded the primary alcohol **23** in 98% yield.[39,40] Alcohol **23** was converted to phenyl sulfone **24** by mesylation, displacement with lithium thiophenylate, and oxidation to the sulfone with MCPBA. This simple three-step

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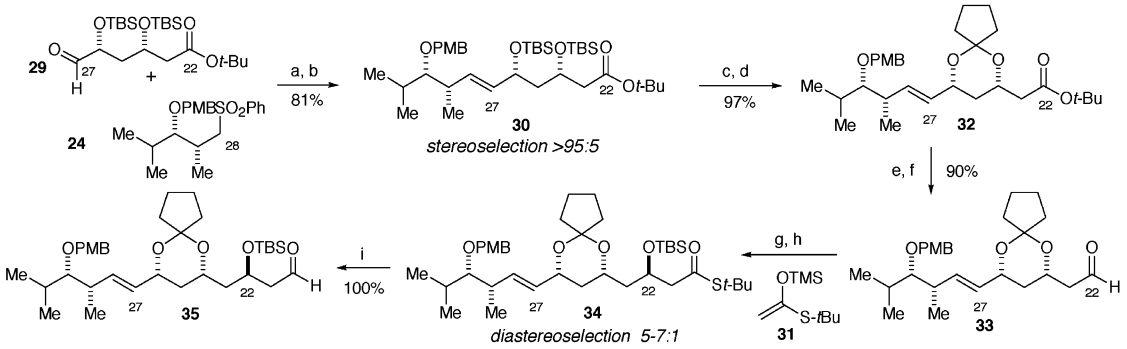
(40) Johansson, R. S. *J. Chem. Soc., Chem. Commun.* **1984**, 201−202.

Scheme 9 [a]



[a] Key: (a) *n*-BuLi, $BF_3{\cdot}OEt_2$, −78 °C, THF; (b) Na/Hg, Na_2HPO_4, −40 °C→ 23 °C, MeOH; (c) HF·pyr, THF; (d) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (e) $LiAlH_4$, THF; (f) Dess−Martin, CH_2Cl_2; (g) $BF_3{\cdot}OEt_2$, **31**, −90 °C, toluene; (h) TBSOTf, 2,6-lutidine, −78°C, CH_2Cl_2; (i) DIBAl−H, −78 °C, toluene.

sequence proceeded in 96% yield without the need for purification of either intermediate.

Synthesis of the $C_{20}-C_{27}$ fragment began with the Lewis acid-catalyzed addition of the Chan's diene analogue **26** to (benzyloxy)acetaldehyde (**25**) (Scheme 8). Utilizing 2 mol % of our previously reported chiral Lewis acid catalyst, [Cu(*S*,*S*)-Phpybox]$(SbF_6)_2$, (eq 3), 500 mg of recoverable ligand afforded 20 g of **27** in 85% yield and >99% ee from **25** and **26**.[17] The protected syn diol **28** was prepared via Et_2BOMe-mediated $NaBH_4$ reduction of **27**, followed by protection of the diol as a bis(TBS) ether **37** in 87% yield for the two steps.[20] A cyclic ketal protecting group for this diol would have been ideal for the synthesis, as it would promote a stereoselective aldol addition in a later reaction. Unfortunately, the proposed Julia fragment coupling onto a C_{27} aldehyde failed with all cyclic protecting groups installed at this position (vide infra). For maximal efficiency and protecting group compatibility, **28** was prepared for immediate coupling to sulfone fragment **24** before further elaboration of the polyacetate region from the ester terminus. Catalytic hydrogenation of **28** proceeded smoothly under forcing conditions (2000 psi H_2, 50 h) to reveal the primary alcohol that was efficiently oxidized using the Dess−Martin periodinane to afford aldehyde **29** in 97% yield for the two steps.[41]

Our initial fragment coupling study in the assemblage of the $C_{20}-C_{30}$ subunit was disappointing. Deprotonation of sulfone **24**, followed by addition of aldehyde **29** did not produce any coupled products (Scheme 9). Regardless of the exact experimental conditions, including choice of metal counterion, solvent, order of addition, and temperature, the sulfone component was always recovered unchanged along with aldehyde decomposition products. Competing enolization of **29** led to substrate decomposition in every instance examined. Similar observations were made in an earlier study when the $C_{24}-C_{26}$ hydroxyls had been protected as an acetonide. Since the problems associated with the Julia olefination stemmed from the excessive basicity of the sulfone anion, it was reasoned that buffering the reaction mixture with a Lewis acid could overcome this problem.[42] Indeed, deprotonation of 1.0 equiv of sulfone **24** with *n*-BuLi followed by sequential addition of 1.0 equiv of $BF_3{\cdot}OEt_2$ and aldehyde **29** provided the desired β-hydroxy sulfones as a mixture of diastereomers. The use of freshly prepared $MgBr_2{\cdot}OEt_2$, rather than $BF_3{\cdot}OEt_2$, afforded equivalent results, but freshly distilled $BF_3{\cdot}OEt_2$ was chosen for ease of use on larger scale reactions. Alternatively, aluminum-based Lewis acids led only to decomposition of starting materials. Functionalization of the β-hydroxysulfone for subsequent elimination was unsuccessful under a variety of conditions. All acetylation and mesylation attempts yielded only recovered starting material. Fortunately, it was eventually found that direct treatment of the hydroxysulfone mixture with 5% Na/Hg amalgam in buffered methanol at −20 °C provided the desired *E*-olefin **30** in 81% yield as a single isomer by ^1H NMR spectroscopy (Scheme 9).

The desire for a synthetically useful level of diastereoselectivity in the projected aldol reaction onto the C_{22} aldehyde necessitated a protecting group exchange, since β-silyloxyaldehydes usually yield poor diastereofacial control.[14] Indeed, aldol reaction of C_{24},C_{26}-bis(TBS) protected aldehyde equivalent of **33** with trimethylsilylketene acetal of *S*-*tert*-butyl thioacetate (**31**) mediated by $BF_3{\cdot}OEt_2$ yielded only 2:1 syn diastereoselectivity. Accordingly, the TBS ethers were cleanly removed (HF·pyridine, THF), and the cyclopentylidene ketal was introduced under mildly acidic conditions (PPTS) to deliver **32** in 97% yield for the two-step sequence. The ester was transformed to the aldehyde in a two-step process by LAH reduction to the alcohol and Dess−Martin oxidation to afford aldehyde **33** in 90% yield. Treatment of **33** in toluene at −110 °C with **31** in the presence of $BF_3{\cdot}OEt_2$ afforded a 5−7:1 inseparable mixture of C_{22}-diastereomers which were immediately silylated with TBSOTf to afford protected thioester **34** in 83% yield. Controlled DIBAl-H reduction of the thioester proceeded quantitatively to deliver the desired aldehyde **35** as a 5−7:1 mixture of diastereomers.

Roxaticin. The final stages of the roxaticin synthesis are summarized in Scheme 10. Formation of the dibutylboron enolate of methyl ketone **19** (NEt_3, Et_2O, −78 °C), followed by addition of aldehyde **35** at −110 °C delivered the aldol adduct **36** in 79% yield as a single epimer at C_{20}, as evidenced by ^1H NMR spectroscopy, along with 15% recovered methyl ketone **19**.[15] It is interesting to note that a kinetic resolution took place over the course of the reaction, affording the desired product in preference to the adduct derived from reaction of the undesired aldehyde epimer. The observed product contained both the 1,5-anti and the 1,3-anti stereochemistry in the polyol array. Therefore, an excess of the isomeric mixture of aldehydes was employed in this reaction, and the recovered aldehyde

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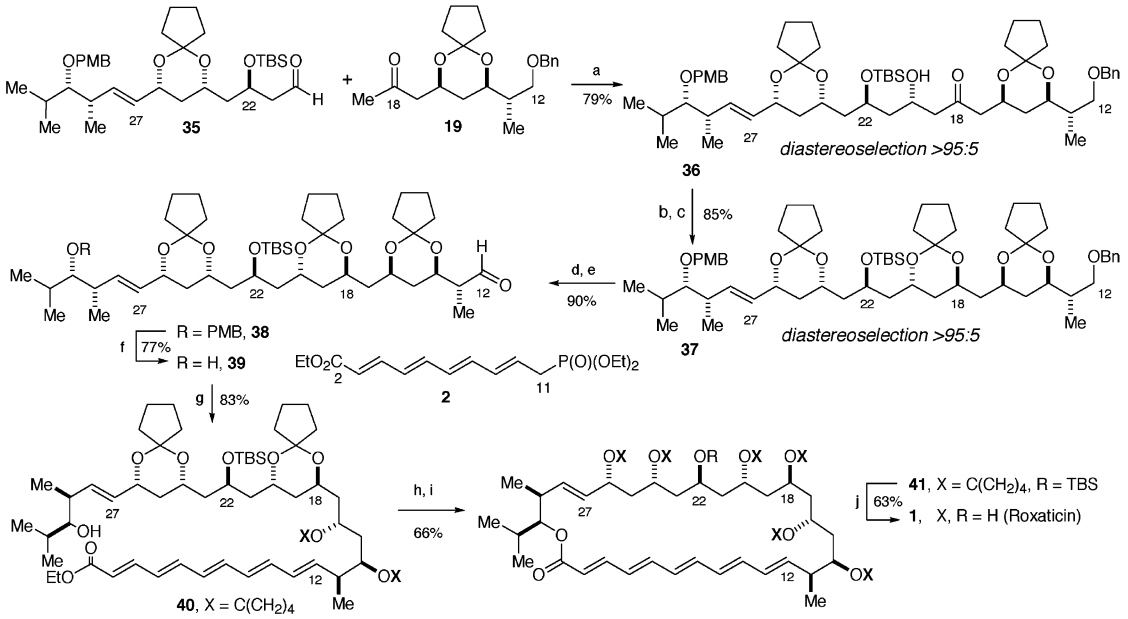
Scheme 10 [a]

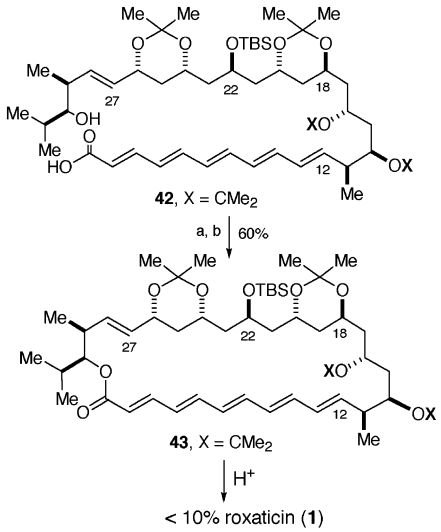


[a] Key: (a) **19** with Bu_2BOTf and NEt_3, −78 °C, then cool to −110 °C, then **35**, Et_2O; (b) $Me_4NBH(OAc)_3$, −25 °C, CH_3CN, AcOH; (c) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (d) LiDBB, −78 °C, THF; (e) Dess−Martin, CH_2Cl_2; (f) DDQ, H_2O, CH_2Cl_2; (g) **2**, LiHMDS, −78 °C, THF; (h) LiOH, THF, H_2O, MeOH; (i) 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, toluene, 23 °C; (j) PPTS, rt, MeOH.

typically was isolated as a 1:1 epimeric mixture at the β-position. The subsequent hydroxyl-directed syn reduction of aldol **36** ($Me_4NHB(OAc)_3$, MeCN/AcOH, −35 °C[19] proceeded smoothly, affording the corresponding diol in good yield (85%) as a single observable diastereomer by 500 MHz ^{1}H NMR spectroscopy. Ketalization afforded fragment **37** in quantitative yield. This fully protected roxaticin precursor contains all the stereocenters present in the natural product and is differentially protected in a manner suitable for the introduction of the polyene fragment **2** and macrolactonization.

Deprotection of the primary C_{12}−benzyl group under reductive conditions (LiDBB, −78 °C)[43,44] followed by Dess−Martin oxidation[41] provided the epimerization-prone aldehyde **38** in 90% yield (Scheme 10). Although Horner-Wadsworth-Emmons reaction with phosphonate **2** (Scheme 3) was the next obvious step, deprotection of the PMB ether would be troublesome in the presence of the oxidizable polyene moiety. Hence, the oxidative deprotection of the C_{30}-methoxybenzyl ether was immediately carried out under buffered conditions (DDQ,[45,46] pH 7 phosphate buffer, CH_2Cl_2) to deliver hydroxy aldehyde **39** in 77% yield. The olefination step was then carried out by deprotonation of phosphonate **2** with freshly prepared LiHMDS, generating the deep purple lithium anion, which when added to aldehyde **39** afforded the conjugated ethyl ester **40** in 83% yield. Ester hydrolysis was straightforward under mild conditions (LiOH/H_2O/MeOH), and the unpurified acid was immediately subjected to Yamaguchi macrolactonization conditions (2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, rt) to provide the macrolactone **41** in 66% isolated yield for the two steps.[47] It was imperative to isolate the mixed anhydride prior to the addition of DMAP to avoid complete decomposition of the substrate, presumably initiated by acid-catalyzed (Et_3NHCl) destruction of the polyene. Final deprotection and product isolation were eventually accomplished with PPTS in MeOH at ambient temperature (<1 h) to deliver synthetic roxaticin **1** in 63% yield after purification by reverse phase HPLC. The synthetic material proved to be identical in all aspects to the natural product.

Scheme 11 [a]



[a] Key: (a) 2,4,6-trichlorobenzoyl chloride, NEt_3, then DMAP, toluene, 6 h, 110 °C.

While this synthesis appeared to proceed with few major obstacles, we encountered significant difficulties when an earlier version of this synthesis was executed with acetonide-based 1,3-diol protection. In a comparison of the lactonization reactions,

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while the macrocyclization of the cyclopentylidine-protected hydroxyacid proceeded at room temperature in toluene (**40**→**41**), the equivalent acetonide-protected hydroxyacid **42** (Scheme 11) required refluxing toluene to achieve formation of the desired macrocycle **43**. More significantly, acetonide deprotection (**43**→roxaticin) proceeded in low yield providing less than 10% of the natural product. The greater lability[48] of the cyclopentylidene ketals proved to be crucial to the isolation of this acid-sensitive natural product in reasonable yield, and this protecting group is recommended to those who undertake the synthesis of related structures.

Conclusion

The objective in this study has been to develop and integrate stereoselective aldol addition reactions (eqs 1−3) into an efficient synthesis of roxaticin. Stereochemical control in these reactions has been derived from the use of either chiral auxiliaries or chiral catalysts. The boron enolate-mediated aldol fragment coupling reaction employed to join the $C_{20}-C_{30}$ aldehyde and $C_{12}-C_{19}$ methyl ketone fragments (Scheme 10) should be an important fragment coupling process in polyene macrolide synthesis, and this reaction has already been used in our syntheses of altohyrtin C[49] and phorboxazole B,[50] as well as by others in their approaches to polyol containing natural products.[51]

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Supporting Information Available: Experimental details and analytical data for all new compounds and comparison data for natural and synthetic roxaticin (PDF) (27 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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