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Total Synthesis of Irciniastatin A (Psymberin)

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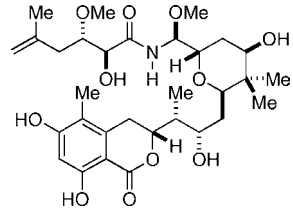
ABSTRACT



The total synthesis of (+)-iriciniastatin A (psymberin) is reported in 19 steps and 6% overall yield. Key reactions include a highly convergent enolsilane−oxocarbenium ion union to generate the C8−C25 fragment and a late-stage coupling of a hemiaminal and acid chloride to complete the synthesis.

In 2004, Pettit and Crews independently reported the isolation of two remarkably potent and selective cancer cell growth inhibitors from the extracts of deep water sponges. Irciniastatin A (**1**) was obtained from *Ircinia ramosa* by Pettit,[1] and psymberin was isolated from *Psammocina* sp. by Crews.[2] The two secondary metabolites were shown to be structurally related on the basis of spectroscopic studies; however, incomplete and conflicting stereochemical analyses precluded a definitive assignment of absolute configuration. Each displayed incredibly powerful and selective cancer cell growth inhibition. Irciniastatin A was reported to exhibit a greater than 10^4 differential in activity across related cell lines. The limited natural abundance and lack of an absolute stereochemical assignment, as well as interest in further exploration of the unique chemotherapeutic profile and mode of action, sparked immediate interest within the synthetic community.

Early reports shed light on the stereochemical ambiguities through fragment synthesis[3] and natural product degradation.[4] Ultimately, it was the seminal total synthesis by DeBrabander[5] that confirmed the absolute configuration and demonstrated that irciniastatin A (**1**) and psymberin were identical. Subsequent reports, including fragment synthesis,[6] a formal synthesis,[7] two total syntheses,[8,9] and two reports of analogue syntheses,[10,11] all offered creative and distinct approaches toward the unique structural elements of irciniastatin A.

Our interest in (+)-irciniastatin A (psymberin) focused on developing a highly diastereoselective and modular synthesis that might be suitable for analogue preparation. Our efforts

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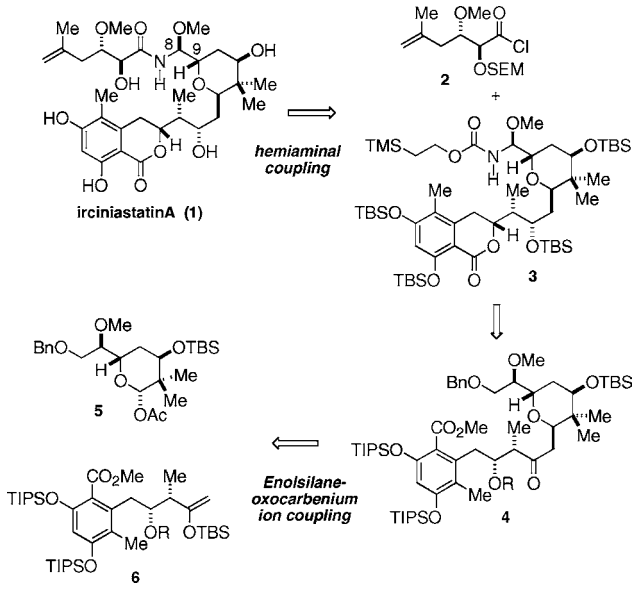
toward (+)-**1** recently culminated in a completed total synthesis that is reported here.

Retrosynthetically (Scheme 1), (+)-irciniastatin A (**1**) was envisioned to arise from two key disconnections. A late-stage attachment of the psymberic acid chain would be accomplished

Scheme 1. Retrosynthetic Analysis of Irciniastatin A



by coupling of acid chloride **2** with hemiaminal **3**, the product of a Curtius rearrangement of the carboxylic acid derived from benzyl ether **4**. This tactic would allow for a highly stereocontrolled entry to the C8 hemiaminal and efficient incorporation of the side chain. Tetrahydropyran **4** would arise from the stereoselective addition of enolsilane **6** to the oxocarbenium ion derived from acetate **5**. These two key disconnections segregate the three major subunits of irciniastatin A (**1**), each of similar size and complexity and accessible in a highly stereocontrolled fashion from standard aldol synthons.

All reported syntheses of the psymberate side chain have relied on functionalizing commercially available chiral pools or enzymatic resolutions. In addition, analogue studies[10,11] have shown the side chain to be required for high activity. Therefore, an enantioselective and highly tunable synthesis of the side chain would be ideal for further investigation of side chain function. We reasoned that an oxazolidinethione asymmetric glycolate aldol reaction[12] would allow for enantioselective entry to the psymberate side chain as well as provide sufficient opportunities for derivitization and

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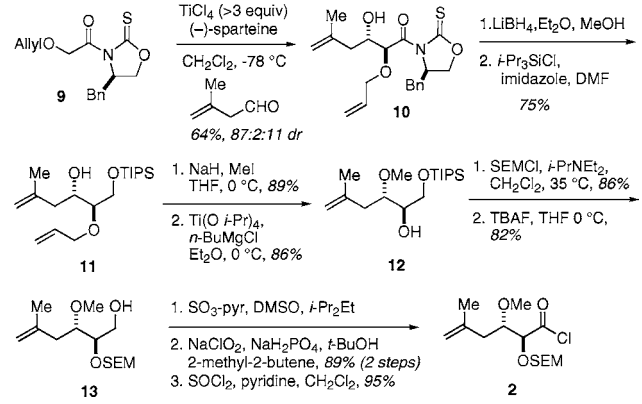
congener synthesis. The synthesis of acid chloride **2** (Scheme 2) began with the known[13] *anti*-aldol[12a] reaction of glycolate

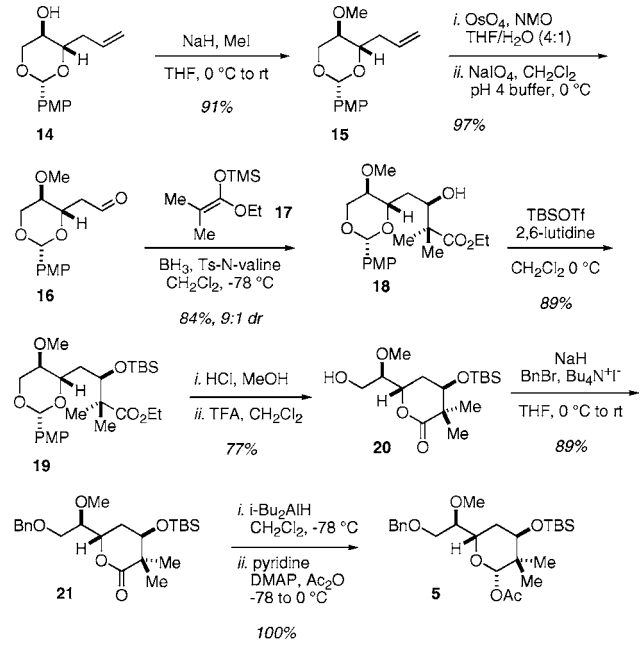
Scheme 2. Synthesis of the Psymberic Acid Side Chain



9 and 3-methyl-but-3-enal to deliver aldol adduct **10** that was converted to known TIPS ether **11**.[13] Methylation of the alcohol was followed by removal of the allyl protecting group under Kulinkovich conditions[13,14] to give alcohol **12**. Protection of alcohol **12** as the SEM ether was followed by selective removal of the primary TIPS ether. The resultant primary alcohol **13** was oxidized under Smith's conditions, giving the corresponding acid over two steps. The acid (9 steps, 28% overall) was converted to acid chloride **2**.

The synthesis of the acetate **5** (Scheme 3) began from known *p*-methoxybenzylidine acetal **14**[15] available from 2-deoxy-D-ribose in two steps. Methylation of alcohol **14** was followed by a dihydroxylation−oxidative cleavage

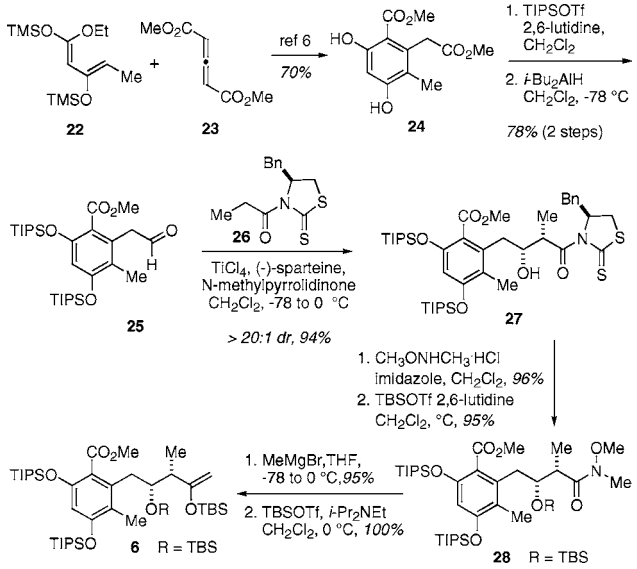
Scheme 3. Synthesis of Acetate **5**



sequence to reveal aldehyde **16**. A catalyst-controlled Kiyooka[16] aldol reaction of aldehyde **16** and enolsilane **17**[17] provided carbinol **18** in 84% yield and 9:1 dr. Protection of alcohol **18** to give TBS ether **19** was followed by acid-catalyzed cyclization to provide a 10:1 mixture of lactone **20** and the corresponding diol, which was converted to lactone **20** by exposure to CF_3CO_2H. Protection of the primary alcohol gave benzyl ether **21** and subsequent one-pot reductive acetylation[18] afforded acetate **5** in quantitative yield (9 steps, 34% overall from 2-deoxy-D-ribose).

The synthesis of enolsilane **6** (Scheme 4) began from known catechol **24**[6,19] prepared by cycloaddition of allene

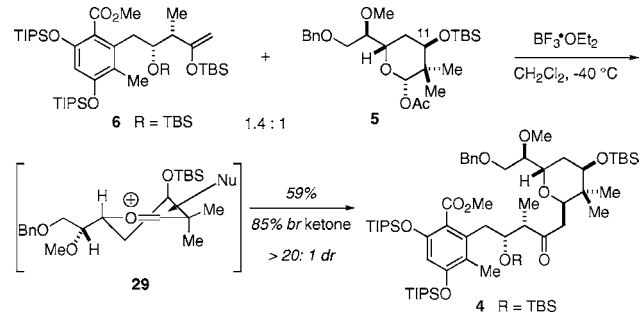
Scheme 4. Synthesis of Enolsilane **6**



23[20] and diene **22**.[21] Protection of catechol **24** as the bis-TIPS ether was followed by selective ester reduction to give aldehyde **25** in 78% yield over 2 steps. An asymmetric propionate aldol[22] reaction of aldehyde **25** and propionyl thiazolidinethione **26** afforded the Evans-*syn*-aldol adduct **27** in 94% yield and >20:1 dr. Direct displacement of the chiral auxiliary with Weinreb's amine was followed by protection of the secondary alcohol as a TBS ether to deliver silyl ether **28**. The methyl ketone prepared from Weinreb's amide **28** was then readily converted to desired enolsilane **6** (7 steps; 66% overall from catechol **24**).

Having devised highly stereocontrolled routes to all three key fragments, the union of enolsilane **6** and acetate **5** was investigated (Scheme 5). Rigorous experimentation revealed that $BF_3{\cdot}OEt_2$ was the optimum Lewis acid and that TBS enolsilane **6** performed better than the corresponding TMS

Scheme 5. Coupling of Acetate **5** with Enolsilane **6**



enolsilane for the assembly of **5** and **6**. Most intriguing, however, was that addition of a solution of enolsilane **6** to a premixed solution of **5** and $BF_3{\cdot}OEt_2$ at −40 °C was required for efficient coupling. The union proceeded with high diastereoselectivity, giving tetrahydropyran **4** as the only detectable diastereomer. The high diastereoselectivity can be rationalized by well precedented[23] pseudoaxial addition of the nucleophile to the oxocarbenium conformer **29**, proceeding through a favorable chairlike conformation. Conformer **29** would also be expected to be favored as a result of through-space stereoelectronic stabilization[23] of the oxocarbenium ion by the axially positioned C11 ether.

With the C8−C25 carbon framework in place, conditions to set the C15 stereocenter were investigated (Scheme 6). Standard achiral reducing agents proved to be nonselective or completely selective for the undesired diastereomer;[24] however, the use of the chiral (R)-CBS[25] agent exclusively provided desired diastereomer **30**[26] in 82% yield. After protection of the secondary alcohol as its TBS ether and cleavage of the benzyl ether, carbinol **31** was oxidized over 2 steps to carboxylic acid **32**. Initial studies showed the one-pot Curtius reaction with (*O*,*O*)-diphenylphosphoryl azide[27] to be ineffective, providing significant quantities of inseparable carbamoyl azide impurity.[28] Therefore, Weinstock's procedure[9,29] was employed to generate the intermediate isocyanate, which under mild conditions using copper(I)

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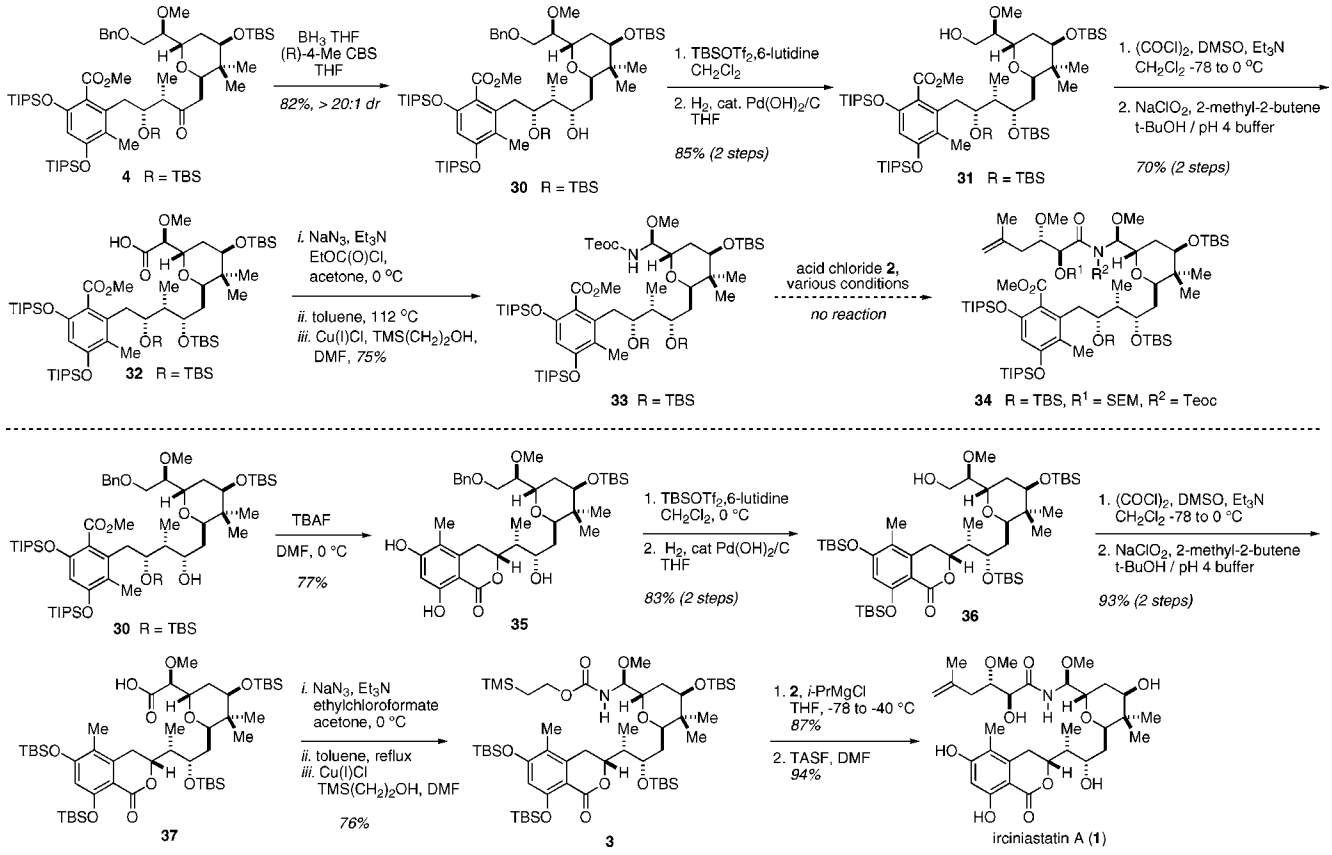
Scheme 6. Completion of the Synthesis of (+)-Irciniastatin A



chloride afforded Teoc-protected hemiaminal **33**.[30] Much to our dismay, a screen of reported conditions[31] for acylation of stucturally related intermediates never yielded *N*-acyl hemiaminal **34**. A survey of the previous syntheses of irciniastatin A finds that all feature a late stage aminal and side chain incorporation with a preformed lactone of the dihydroisocoumarin. Albeit unlikely that such remote functionality should have any effect on the hemiaminal coupling, the limited number of available options warranted pursuit of this lead.[32]

Strategically, after the CBS reduction, the lactone was formed concomitantly with removal of the TBS ether to give **35**, adding only one synthetic step over the original plan (bottom of Scheme 6). An analogous sequence of TBS protection of the C15 carbinol and hydrogenolysis of the benzyl ether gave carbinol **36**, which was subjected to a two-step oxidation to acid **37**. Acid **37** was subjected to the previously established Curtius conditions to give hemiaminal **3**. With hemiaminal **3** featuring the lactonized dihydroisocoumarin, it was found that *i*-PrMgCl, a base not previously used for this transformation, successfully effected reaction with acid chloride **2** in a remarkable 87% yield. Finally, global deprotection with TASF in DMF at 50 °C provided (+)-irciniastatin A (**1**) in 94% yield.

In summary, the total synthesis of (+)-irciniastatin A (**1**) was completed in 19 steps with a 6% overall yield from 2-deoxy-D-ribose. The successful application of this strategy allowed for rapid assembly of the three key fragments with high diastereocontrol. Studies directed toward analogue synthesis and further evaluation of the antitumor activity of irciniastatin A are underway in collaboration with the Lineberger Comprehensive Cancer Center.

Acknowledgment. Financial support from the National Institute of General Medical Sciences (GM60567) is gratefully acknowledged.

Supporting Information Available: Experimental details and spectral data for new compounds as well as irciniastatin A. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) NOE experiments on related compounds by DeBrabander indicate a close spatial relationship between these two regions of the molecule (see ref 11).