VIP Natural Product Synthesis

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Highly Efficient Stereocontrolled Total Synthesis of (+)-Upial**

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(+)-Upial (**1**), isolated from the sponge *Dysidea fragilis* of Kaneohe Bay (Hawaii), was found to be a nonisoprenoid sesquiterpene aldehyde lactone containing the rare bicyclo-[3.3.1]nonane skeleton.[1] Its structure was originally proposed on the basis of spectroscopic analyses of the natural product and the products of its degradation and chemical transformations (Figure 1).[1] The absolute configuration of upial

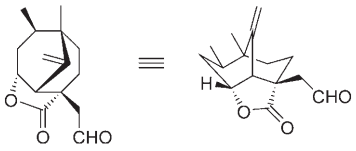


Figure 1. Structure of (+)-upial (**1**).

was unambiguously determined by the total synthesis of its enantiomer starting from a readily accessible chiral source, (−)-carvone.[2] Synthesis of the naturally occurring(+)-upial was first achieved by Yamada and co-workers.[3] In the synthesis, a double Michael reaction of an (*E*)-α,β-unsaturated ester with the enolate of 6-methyl-3-methoxymethoxy-2-cyclohexenone and subsequent fragmentation of the resulting adduct were the key reactions used to construct the basic carbon framework. Snider and O'Neil also synthesized racemic upial whereby oxidative free-radical cyclization of 4-(3-hexenyl)-1,3-cyclohexanedione was employed as a key step.[4]

As a result of its architecturally intriguing bicyclic skeleton, upial and related analogues **2**–**4** (Figure 2) have received considerable attention from synthetic chemists over the years.[5] The crucial step for the synthesis of **1** is the stereocontrolled construction of a bicyclo[3.3.1]nonane ring system with five stereogenic carbon centers as well as facile introduction of the *exo*-methylene unit.

Our own interest in **1** grew out of a desire to find an entirely new route for its total synthesis. In analyzing the

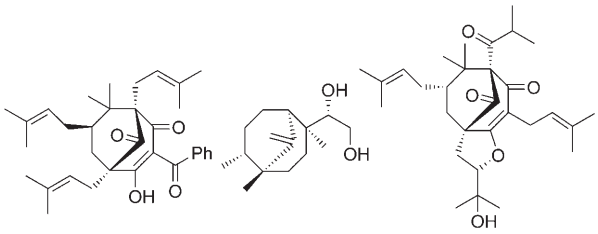
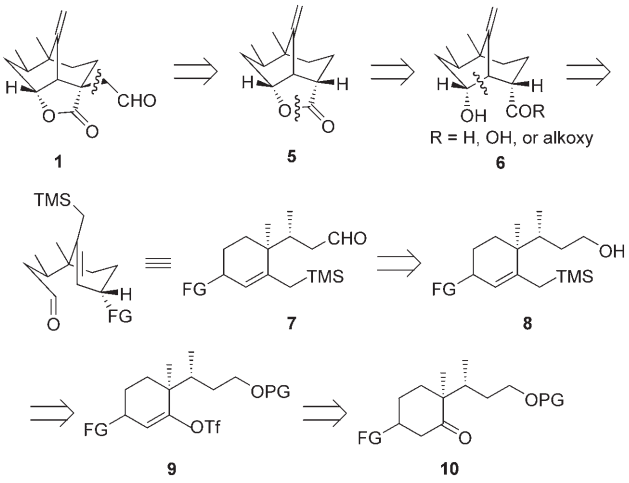


Figure 2. Structures of natural products with a bicyclo[3.3.1]nonane ring system.

structure of **1** for retrosynthetic disconnection, we focused on formation of the bicyclo[3.3.1]nonane ring system and the *exo*-methylene function simultaneously. Accordingly, either the Sakurai reaction[6] or an intramolecular carbonyl–ene reaction[7] were candidates for transformation of a corresponding allyl silane derivative **7** possessing an appropriate functional group, which could be converted into a carbonyl function at the later stage of the synthesis (Scheme 1). Moreover, the acetaldehyde unit of **1** could be introduced to lactone **5** at the final stage of the synthesis, and lactone **5** could be secured from hydroxy-carbonyl compound **6**. The key aldehyde **7** would be obtained from a corresponding alcohol **8** by oxidation. Installation of an allyl silyl group would be achieved by coupling triflate **9** with (trimethylsilylmethyl)magnesium chloride in the presence of a palladium catalyst.[8] Finally, **9** could readily be obtained from ketone **10**.

In view of these considerations, preparation of allyl silane aldehyde **20** as the key precursor for a cyclization reaction was



Scheme 1. Retrosynthetic analysis of (+)-upial (**1**). FG = functional group, PG = protecting group, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

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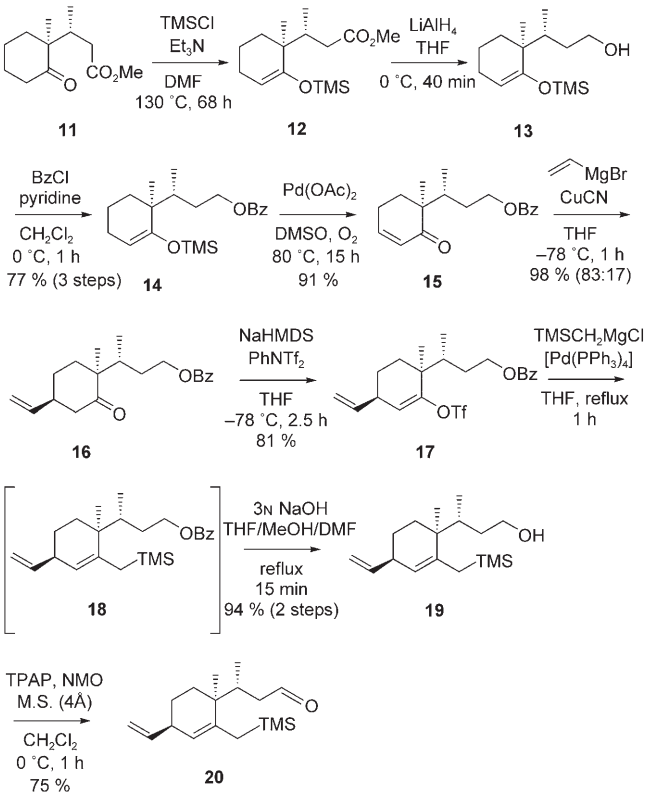
achieved as follows (Scheme 2): The optically active ketone **11**[9] was converted into silyl enol ether **12**, which upon reduction with lithium aluminum hydride afforded alcohol **13**. After protection of the hydroxy group of **13**, the resulting



Scheme 2. Preparation of the key aldehyde (**20**). Bz = benzoyl, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, M.S. = molecular sieves, NMO = 4-methylmorpholine *N*-oxide.

benzoate **14** was subjected to the improved Ito–Saegusa oxidation[10] to give enone **15**. A vinyl group was introduced at the β-position of the enone moiety as a synthetic equivalent to the carbonyl function because previous studies had shown that an attempted preparation of allyl silane derivatives bearing a cyano group or oxo function at this position did not give the desired compounds.[11]

Accordingly, enone **15** was treated with vinylmagnesium bromide in THF at −78 °C in the presence of copper(I) cyanide to afford ketone **16** as an inseparable mixture of diastereoisomers in a ratio of about 5:1 (98% yield). Although the stereochemistry of the vinyl group could not be determined at this stage, it was assumed that the major product had an *S* configuration arising from an axial attack of the vinyl group on enone **15**. Significantly, the stereoselectivity of the conjugate addition of the vinyl group to **15** was influenced by the presence of a methyl group on the side chain. When a similar addition was carried out for the compound without a methyl group on its side chain, the ratio of products was found to be approximately 1:1. Ketone **16** was treated with *N*-phenyltriflimide and sodium hexamethyldisilazide (NaHDMS), and the resulting triflate **17** was coupled with (trimethylsilylmethyl)magnesium chloride in the presence of tetrakis(triphenylphosphine)palladium to afford allyl silane derivative **18**. Deprotection of the benzoyl group of **18** using 3 N NaOH gave the alcohol **19**, which upon oxidation with tetrapropylammonium perruthenate (TPAP) afforded the desired aldehyde **20**.[12]

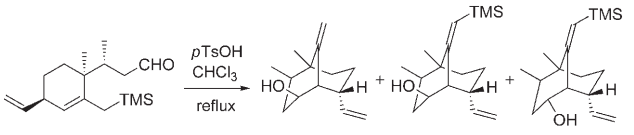
At this stage a study was carried out to determine the best conditions for construction of the bicyclic system by using either the Sakurai reaction or an intramolecular carbonyl–ene reaction. Although difficulties were initially encountered with the conversion of **20** into **21** (for example, attempted cyclization with a Lewis acid such as zinc chloride, boron trifluoride etherate, or tin(IV) chloride gave the desired compound in only moderate yields), treatment of **20** with 0.2 mol% of *para*-toluenesulfonic acid (*p*TsOH) in refluxing chloroform afforded the cyclization products **21**, **22**, and **23** in 85% yield in a ratio of 28:67:5 (Table 1). This result clearly indicated that the cyclization would proceed through an intramolecular carbonyl–ene reaction. When the reaction was carried out with 10 mol% of *p*TsOH in refluxing chloroform for 15 minutes, the desired compound **21** was isolated stereoselectivly in 96% yield (Table 1).[13] In this conversion, the stereochemistry of the secondary hydroxy group of **21** was again controlled by the presence of a vinyl group. The stereochemistry of the product was unambiguously determined on the basis of 2D NMR spectroscopy and NOE experiments.

It should also be noted that the presence of a trimethylsilyl group seemed to be essential for the carbonyl–ene reaction. Our preliminary experiment showed that a structurally related model compound without a trimethylsilyl group did not give any desired compound under similar reaction conditions.

The stereochemistry of the hydroxy group of **21** was inverted in two steps by oxidation with TPAP and subsequent reduction of the resulting ketone **24** with sodium borohydride reduction to give **25** (Scheme 3).

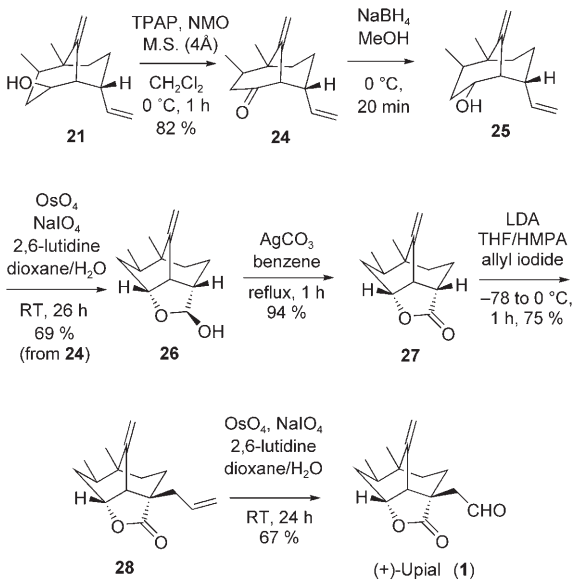
Finally, the improved Lemieux–Johnson oxidation of **25** gave lactol **26**.[14] In the oxidation, a site-selective dihydroxylation of the carbon–carbon double bond was observed. Further oxidation of **26** with Fetizon reagent provided the known lactone **27**. The specific optical rotation of **27** was identical to that reported in the literature[2] (although its spectroscopic data were not mentioned). To complete the total synthesis of the target compound **1**, lactone

Table 1: Intramolecular carbonyl–ene reaction of aldehyde **20** with *p*TsOH.



*p*TsOH [mol%]	*t* [h]	Total yield [%]	Ratio (**21**:**22**:**23**)
0.2	0.5	85	28:67:5
0.5	1.0	74	41:55:4
10	0.25	96	100[a]:0:0

[a] *exo*:*endo* ratio (96:4) was determined by ^{1}H NMR spectroscopy.



Scheme 3. Synthesis of (+)-upial (**1**). HMPA = hexamethylphosphoramide.

27 was alkylated with allyl iodide in the presence of lithium diisopropylamide (LDA) to give allyl compound **28**, which upon Lemieux–Johnson oxidation afforded (+)-upial (**1**) (Scheme 3).

In conclusion, we have established a concise total synthesis of (+)-upial (**1**). The key step of this synthesis is an intramolecular carbonyl–ene reaction, in which stereocontrolled construction of a bicyclo[3.3.1]nonane ring system with five asymmetric carbon centers and facile introduction of the *exo*-methylene unit were achieved in one step. In 15 steps, this synthesis afforded the target compound **1** in 10.2% overall yield from the readily accessible known starting material **11**. We believe that this synthetic strategy has great potential application for the synthesis of a wide range of natural products bearing such bicyclic systems.

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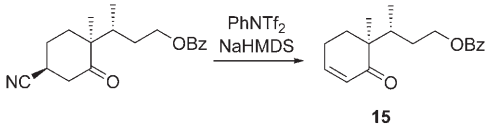
[11] Preparation of a cyano derivative corresponding to **17** was attempted; however, enone **15** was isolated instead of a desired triflate as the reaction product.



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Moreover, a structurally related aldehyde with an ethylenedioxy group instead of a vinyl group in **20** was also synthesized. However, attempted intramolecular carbonyl–ene reactions leading to a bicyclo[3.3.1]nonane skeleton under various reaction conditions failed.
[12] Another diastereoisomer was separated during the preparation of triflate **17**.
[13] The reaction conditions for an intramolecular carbonyl–ene reaction were carefully investigated prior to this reaction by using the devinyl compound of **20** as a model study.
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