Regio- and Enantioselective Prenyl Anion Transfer: Application to the Total Synthesis of (−)-Rosiridol**

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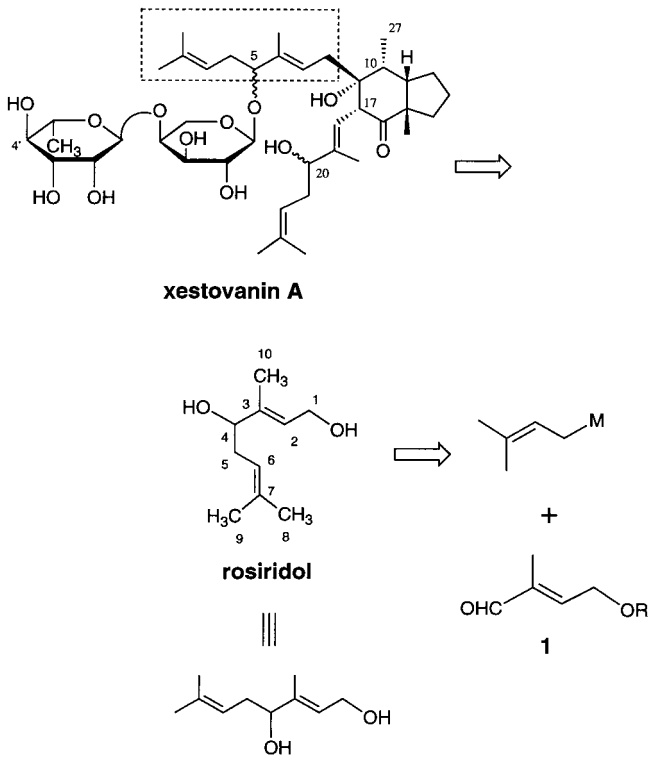
Dedicated to Professor E. J. Corey on the occasion of his 70th birthday

Monoterpenes have long been recognized as invaluable chiral precursors for the synthesis of various classes of natural products.[1] Many methodologies directed at the stereoselective synthesis of monoterpenes have been described. In recent years, stereoselective C–C bond forming reactions between allyl anions and carbonyl electrophiles have received a lot of attention.[2] We now describe a novel regio- and enantioselective prenyl anion addition to aldehyde **1** and its application to the first total synthesis of the monoterpene (−)-rosiridol.

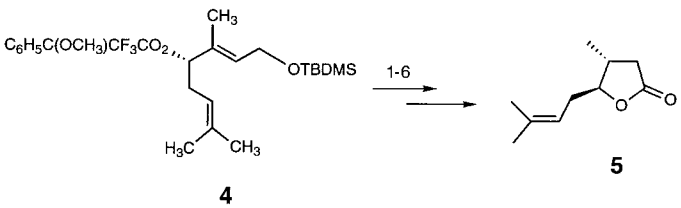
Our synthesis of xestovanin A[3] required the monoterpene rosiridol as a key intermediate (Scheme 1). Rosiridol has been isolated from several natural sources.[4] Although the structure of rosiridol had been reported, its absolute configuration remained unknown and to this date no total synthesis has been developed.[5, 6] In 1993 Manns isolated a new monoterpene from the leaves of *Cunila spicata* Benth (Lamiaceae) that bore close resemblance to the diacetate of rosiridol.[7] On the basis of this similarity the new monoterpene was named isorosiridol diacetate. However, there was a striking difference in the chemical shift of the C4 proton of rosiridol diacetate prepared from natural rosiridol ($\delta = 5.10$) and the C4 proton of this new monoterpene diacetate ($\delta = 5.70$). Based on de Haan's spectroscopic method and the ^{13}C NMR chemical shift of the C3 methyl group, Manns concluded that isorosiridol diacetate is (2*E*)-3,7-dimethylocta-2,6-diene-1,4-diol diacetate and that Kurkin's rosiridol could in fact be the *Z* isomer.



Scheme 1. Retrosynthesis of xestovanin A via rosiridol.

Retrosynthetic analysis indicates that rosiridol may be prepared by prenylation of aldehyde **1**.[8] Such carbonyl alkylations using prenyl metal anions are inherently problematic since both α and γ adducts are formed during the reaction, and in general, the γ adduct dominates.[9] Very few examples of α-selective carbonyl alkylations using prenyl anion are known.[10, 11] In fact, a practical and enantioselective α-alkylation of prenyl anion to aldehydes has never been reported.

We found that addition of the prenyl Grignard reagent, prenyllithium, or prenylzinc to aldehyde **1** provided the γ adduct **3** predominately (Table 1, entries 1–13). However, when prenylzinc was allowed to react with aldehyde **1** in the presence of HMPA for three days (THF, reflux), the α adduct **2** formed predominately (Table 1, entry 14).[12] Clearly, this is an equilibrium process in which the kinetic product **3** rearranges to the thermodynamic product **2** after prolonged heating (entries 13 and 14). Treatment of racemic alcohol **2** with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher chloride) afforded the corresponding Mosher esters, which were separated by HPLC and deprotected (KOH, MeOH; HF, THF, 90%) to give (−)- and (+)-rosiridol. The ^1H and ^{13}C NMR spectra of synthetic (−)-rosiridol are identical to those of natural (−)-rosiridol reported by Kurkin et al.[13] These results provide strong evidence that (−)-rosiridol is in fact (2*E*)-3,7-dimethylocta-2,6-diene-1,4-diol. To determine the absolute configuration at C4 of rosiridol, the Mosher ester **4** of (−)-rosiridol was converted into (−)-eldanolide (**5**) in six steps and 30% overall yield (Scheme 2).[14] Hence the structure of (−)-rosiridol can be assigned as (*S*)-(2*E*)-3,7-dimethylocta-2,6-diene-1,4-diol.



Scheme 2. 1. KOH, MeOH; 2. Ac_2O, Et_3N, 4-dimethylaminopyridine (DMAP), CH_2Cl_2; 3. HF, THF; 4. MnO_2, CH_2Cl_2; 5. MnO_2, KCN, MeOH; 6. $NaBH_4$, cat. $NiCl_2$, MeOH.

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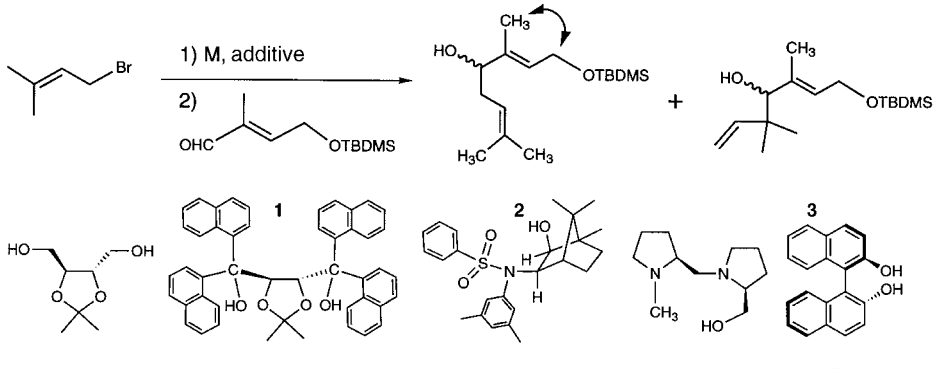
Table 1. Reaction of prenyl anion and aldehyde **1**.



A **B** **C** **D** **E**

Entry	M	Additive [equiv]	Solvent [h]	*T*	*t*	Products[b] **2**[a]:**3**	*R*/*S*(**2**)	Total yield [%][c]
1	Mg	0	THF	− 78°C	2	0:100		85
2	Mg	0	THF	reflux	2	0:100		85
3	Mg	0	THF	reflux	72	4:96		85
4	Mg	0	Et_2O	reflux	2	0:100		83
5	Mg	0	Et_2O	reflux	72	4:96		83
6	Li	0	THF	− 78°C	2	1:99		91
7	Li	0	THF	reflux	72	1:99		90
8	Zn	0	THF	− 78°C	2	1:99		93
9	Zn	0	THF	reflux	2	1:99		92
10	Zn	0	THF	reflux	72	7:93		90
11	Zn	0	Et_2O	reflux	2	0:100		89
12	Zn	0	Et_2O	reflux	72	6:94		87
13	Zn	HMPA (15)	THF	reflux	2	6:94		89
14	Zn	HMPA (15)	THF	reflux	72	**94:6**		89
15	Zn	**A** (1.5), HMPA (15)	THF	reflux	72	94:6	40/60	90
16	Zn	**A** (1.0), HMPA (15)	THF	reflux	72	94:6	43/57	90
17	Zn	**A** (0.2), HMPA (15)	THF	reflux	72	94:6	45/55	90
18	Zn	**B** (1.5), HMPA (15)	THF	reflux	72	94:6	19/81	89
19	Zn	**B** (1.0), HMPA (15)	THF	reflux	72	94:6	25/75	89
20	Zn	**B** (0.2), HMPA (15)	THF	reflux	72	94:6	31/69	89
21	Zn	**C** (1.5), HMPA (15)	THF	reflux	72	94:6	**3/97**	87
22	Zn	**C** (1.0), HMPA (15)	THF	reflux	72	94:6	12/88	87
23	Zn	**C** (0.2), HMPA (15)	THF	reflux	72	94:6	14/86	87
24	Zn	**D** (1.5), HMPA (15)	THF	reflux	72	94:6	57/43	86
25	Zn	**D** (1.0), HMPA (15)	THF	reflux	72	94:6	56/44	86
26	Zn	**D** (0.2), HMPA (15)	THF	reflux	72	94:6	54/46	86
27	Zn	**E** (1.5), HMPA (15)	THF	reflux	72	94:6	49/51	84
28	Zn	**E** (1.0), HMPA (15)	THF	reflux	72	94:6	49/51	84
29	Zn	**E** (0.2), HMPA (15)	THF	reflux	72	94:6	50/50	84

[a] The relative configuration of **2** was determined unambiguously by a 2D NOESY experiment. The spectrum, which shows key correlations between the protons on C1 and C10, supports the structure depicted in this table. [b] Optical purity assayed by preparation of the (*R*)-MTPA esters and analyzed by HPLC. [c] Yield of isolated product based on starting aldehyde.

Enantioselective alkylation of aldehydes using organozinc compounds in the presence of chiral Lewis acids is well known.[15] However, most Lewis acids decompose or lead to polymerization in refluxing THF. Since our prenylzinc reagent was stable under the reaction conditions, we postulated that addition of a chiral ligand to the reaction mixture may help induce some enantioselectivity in this already highly regioselective reaction. Various chiral ligands were employed and the corresponding enantiomeric excesses are summarized in Table 1 (entries 15 – 29). The best enantioselectivies were obtained with ligand **C**.[16] The use of catalytic amounts of chiral ligand did not affect the yield of the reaction; however, the enantioselectivity dropped slightly when substoichiometric amounts of ligand were used (entries 21 – 23).

Some preliminary experiments were conducted to shed light on the origin of the high enantioselectivity in this reaction. Racemate (±)-**3** was resolved by chiral HPLC (Daicel chiral OD column) and the individual enantiomers were subjected to the reaction conditions. Heating (+)-**3** in refluxing THF for 72 hours in the presence of RZnI and HMPA and in the absence of a chiral ligand produced (±)-**2**. However, when (±)-**3** was subjected to the same reaction conditions in the presence of chiral ligand **C**, adduct **2** was isolated with excellent enantiomeric excess (94% *ee*). The detailed mechanism of this reaction is unknown. However, the high enantioselectivity of **2** may be rationalized under the assumption that **3** is formed by a fast and reversible process whereas **2** is the product of a slow but irreversible reaction.

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Experimental Section

To a suspension of zinc (200 mg, 3.06 mmol) in dry THF (10 mL) was added 4-bromo-2-methyl-2-butene (200 mg, 1.34 mmol), and the solution was stirred at room temperature for 1 h. The solution was filtered through a Schlenk filter and kept under argon for the following reaction. To a solution of (1*R*,2*S*,3*R*)-(+)-3-[*N*-benzenesulfonyl-*N*-(3,5-dimethylphenyl)amino]-2-bornanol (116 mg, 0.28 mmol) in dry THF (5 mL) was added the solution of prenylzinc bromide prepared above and the solution was stirred at room temperature for 15 min. The solution was treated with aldehyde **1** (40 mg, 0.19 mmol) and HMPA (0.5 mL, 2.87 mmol) and was heated to reflux for 72 h. A saturated aqueous solution of NH_4Cl (5 mL) was added into the reaction mixture. The solution was diluted with EtOAc (50 mL), washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with EtOAc/hexane (5/95) ($R_f = 0.38$ in EtOAc/hexane, 10/90) to give alcohol **2** as a colorless oil (47 mg, 87 % yield). IR (neat): $\tilde{\nu} = 3382$, 2930, 2921, 2847, 1466, 1378, 1254, 1107, 1061, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 5.53$ (t, $J =$ 5.5 Hz, 1H), 5.09 (t, $J = 7.2$ Hz, 1H), 4.21 (d, $J = 6.0$ Hz, 2H), 3.98 (t, $J =$ 5.5 Hz, 1H), 2.20 – 2.27 (m, 2H), 1.70 (d, $J = 1.0$ Hz, 3H), 1.62 (s, 6H), 1.59 – 1.63 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 137.88$ (C), 134.81 (C), 125.97 (CH), 119.91 (CH), 76.59 (CH), 60.01 (CH_2), 34.02 (CH_2), 25.94 ($3 \times CH_3$), 25.82 (CH_3), 18.34 (C), 17.93 (CH_3), 12.03 (CH_3), – 5.13 ($2 \times CH_3$); MS: *m*/*z* (%): 284 (M^+, 1), 215 (48), 157 (23), 83 (100), 75 (92), 73 (62), 70 (25), 69 (28); HRMS calcd for $C_{16}H_{32}O_2Si$ (M^+): 284.2172; found: 284.2177.

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[12] Alcohol **2** was converted into its THP derivative (HF, THF; dihydropyran (DHP), H^+; 82 %) and into rosiridal (1. Ac_2O, Et_3N, DMAP, CH_2Cl_2; 2. HF, THF; MnO_2, CH_2Cl_2; 76 %). Both compounds were identical in all aspects with those reported in the literature.[5, 6]
[13] The structure of rosiridol was further confirmed unambiguously by NOESY, COSY, HMQC, DEPT, and HMBC experiments. $[\alpha]_D^{25} = -7.1$ ($c = 0.4$ in acetone); lit.: $[\alpha]_D^{25} = -7.7$ ($c = 1.0$ in acetone).[4]
[14] This spectroscopic data of this product are identical with the data reported earlier. $[\alpha]_D^{25} = -52.3$, ($c = 1.4$ in EtOH); lit.: $[\alpha]_D^{25} = -52.4$ ($c = 1.5$ in EtOH); J.-P. Vigneron, R. Méric, M. Larchevêque, A. Debal, *Tetrahedron Lett.* **1982**, *23*, 5051.
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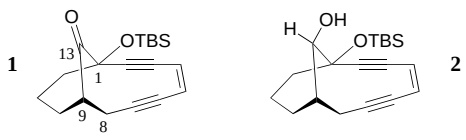
Actuating Cycloaromatization of a Bicyclo[7.3.1]enediyne by Annelation: An Example of Inverse Dependence on Bridge Atom Hybridization**

Michael H. Nantz,* David K. Moss, John D. Spence, and Marilyn M. Olmstead

The calicheamicin and esperamicin enediynes[1] have inspired numerous synthetic and mechanistic studies aimed toward understanding their DNA-cleaving activity.[2] In addition to natural calicheamicin γ_1^I,[3] many structural mimics have been synthesized and shown[4] to undergo the principal transformation responsible for the biological activity, Bergman cycloaromatization[5] of the 1,5-diyn-3-ene unit. We have been especially intrigued by the work of Magnus et al. who first determined the reactivity of bicyclo[7.3.1]enediyne analogues.[6] They showed that the bicyclo[7.3.1] ring of **1** is resistant to enediyne cycloaromatization at ambient temperature and reacts slowly[7] at 71 °C to form the corresponding C(2)–C(7) benzenoid product. In contrast, a change in the hybridization of the one-carbon bridge (C13) from sp^2 to sp^3 (**1** → **2**) was shown to effect a dramatic increase in the rate of cycloaromatization.[8] The tendency toward cycloaromatization was attributed to strain attenuation. These observations point toward the possibility of devising a bicyclo[7.3.1] model system wherein rehybridization of the one-carbon bridge may



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