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COMMUNICATIONS

Published on Web 02/11/2005

Total Synthesis of (+)-Allocyathin B_2

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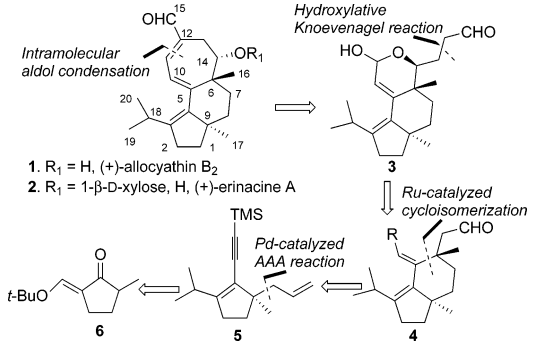
Received October 23, 2004; E-mail: bmtrost@stanford.edu

In 1979, Ayer and co-workers reported the structure of (+)-allocyathin B_2 (**1**, Scheme 1), a metabolite isolated from the fruit bodies of *Cyathus earlei* Lloyd, which possesses an unusual angularly fused 5−6−7 tricyclic framework with a highly unsaturated trienal motif and 1,4-anti quaternary methyl groups.[1a] This compound belongs to a family of diterpenes named cyathins, which were isolated from related species in the 1970s by the Ayer group.[1] These terpenoids exhibit interesting biological activities against actinomycetes, Gram-postitive and Gram-negative bacteria, as well as some fungi.[1b] In 1994, a D-xylose conjugate of allocyathin B_2, erinacine A (**2**, Scheme 1), which is a potent stimulator of nerve growth factor synthesis, was also isolated from the mycelia of *Hericum erinaceum* by Kawagishi.[2] The unique synthetic challenges and therapeutic relevance provided by these molecules attracted intense efforts from a number of research teams since the disclosure of their structures,[3] although only the groups of Snider and Tori have completed the racemic synthesis of allocyathin B_2, in 1996 and 1998.[4]

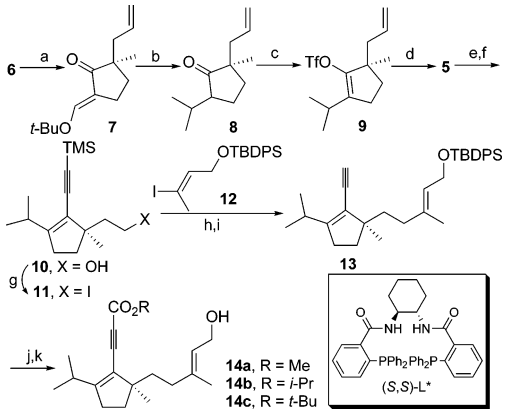
Our recent development of the palladium-catalyzed asymmetric allylic alkylation (AAA) of prochiral ketone enolates[5] and its successful application in the synthesis of hamigeran B allowed us access to ketone **8** in good yield and excellent enantiopurity from compound **6** (Scheme 2).[6] Subsequent conversion to triflate **9** was implemented by treatment of ketone **8** with LDA and $PhNTf_2$.[7] A Sonogashira reaction between triflate **9** and TMS−acetylene generated enyne **5** smoothly.[8] The allyl side chain was oxidatively cleaved (OsO_4, NMO; $NaIO_4$), reduced ($NaBH_4$), and iodinated (PPh_3, I_2, imidazole) to produce compound **11** in good overall yield. A Pd-catalyzed Negishi sp^3-sp^2 coupling reaction of alkyl iodide **11** after conversion to its zinc derivative and vinyl iodide **12**[9] followed by monodesilylation (K_2CO_3, MeOH) furnished terminal alkyne **13**.[10] Esters **14a**−**c** were prepared in two steps from compound **13** in a straightforward fashion involving acylation and deprotection (Scheme 2). This set the stage for the pivotal diastereoselective Ru-catalyzed cycloisomerization.[11]

Under our optimized conditions, the reaction of compound **14a** generated a separable 1.2:1 mixture of two geometrical isomers **15a** and **16a** in satisfactory yield along with a hydroxyl group transposition byproduct, alcohol **17a** (Scheme 3). Gratifyingly, this reaction proceeded with excellent stereocontrol, and only the desired 1,4-anti products were detected.[12] It is also worth noting that this is the first reported double bond isomerization in enyne cycloisomerization reactions to form six-membered rings.[13] The products are stable to the reaction conditions. Two scenarios were envisaged to rationalize the above observation. Presumably, initial oxidative cycloruthenation and β-hydride elimination produce the vinylruthenium hydride **18**, which is in equilibrium, via the hydridoruthenium allenolate, with **19** (Scheme 3).[11] The argument that the reaction outcome reflects the stability of intermediates **18** and **19** would be unlikely considering the relative size of the vinyl ester and the CpRu. In comparison, we favor the alternative of a typical Curtin-Hammett situation. If reductive elimination is slower than

Scheme 1. Retrosynthetic Analysis

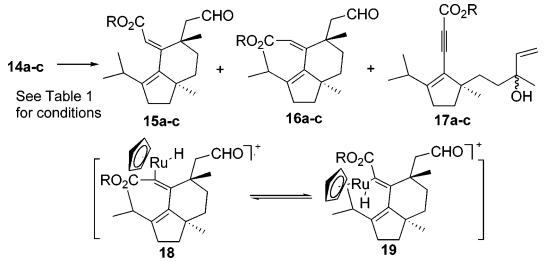


Scheme 2. Syntheses of Substrates **14a**−**c**[a]



[a] (a) LDA, $[(\eta^3\text{-}C_3H_7)PdCl]_2$ (0.5 mol %), (*S*,*S*)-L* (1 mol %), allyl acetate, Me_3SnCl, *t*-BuOH, 83%, 95% ee; (b) Me_2CuLi, −20 °C to room temperature, 86%; (c) LDA, $PhNTf_2$, 96%; (d) $Pd_2(dba)_3CHCl_3$ (2.5 mol %), PPh_3 (20 mol %), CuI (5 mol %), TMS−acetylene, $BuNH_2$, 50 °C, 85%; (e) OsO_4 (1 mol %), NMO; $NaIO_4$, 87%; (f) $NaBH_4$, 94%; (g) PPh_3, I_2, ImH, 97%; (h) *t*-BuLi, $ZnCl_2$, −78 °C to room temperature, then $Pd(PPh_3)_4$ (5 mol %), **12**; (i) K_2CO_3, MeOH, 74% from **11**; (j) *n*-BuLi, $ClCO_2Me$ (**14a**), $ClCO_2i$-Pr (**14b**), $(Boc)_2O$ (**14c**), −78 °C to room temperature, 99%; (k) TBAF, 52−55%.

Scheme 3. Ru-Catalyzed Cycloisomerization



olefin isomerization, it is imaginable that intermediate **19** undergoes faster reductive elimination than **18** to maximize relief of strain energy in the transition state. That means it does not matter which isomer is favored in the equilibrium; the reactive intermediate **19** leads to the major product **15**. This also explains our observation

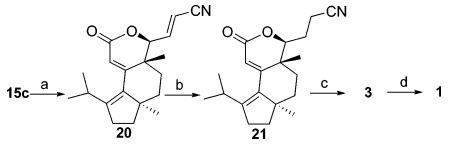
10.1021/ja0435586 CCC: $30.25

Table 1. Ru-Catalyzed Cycloisomerization[a]

entry	substrate	yield (**15** + **16**) %	**15**/**16** ratio
1	**14a**	62 (and 30% **17a**)	1.2:1[c]
2	**14b**	60[b]	1.5:1[c]
3	**14c**	55[b]	6.7:1[c]

[a] All reactions were performed with 20 mol % $CpRu(CH_3CN)_3PF_6$ and 100 mol % DMF in 2-butanone (0.1 M) at room temperature for 2 h. [b] Yields of **17b** and **17c** were not determined. [c] Ratio was determined after isolation. Both geometrical isomers were obtained as single diastereomers.

Scheme 4. Synthesis of (+)-Allocyathin B_2[a]



[a] (a) $PhS(O)CH_2CN$, piperidine, 75%; (b) 10% Pd/C, H_2, 83%; (c) DIBAL−H; (d) KOH, MeOH, 60 °C, 51% from **21**.

that *tert*-butyl ester **14c** gave the highest selectivity as the most relief was achieved in this case.

Since *Z*-isomer **16** is not suitable for the subsequent cyclization to form the seven-membered ring, we faced the challenge to further increase the ratio of compound **15**. If the rationale shown in Scheme 3 holds true, we reasoned that by increasing the size of the ester we might be able to attenuate the strain and thus promote the double bond isomerization. Indeed, we observed a drastic improvement in the ratio of compound **15** by changing methyl ester to *tert*-butyl ester without compromising the conversion and the diastereoselectivity (Table 1). Eventually compound **15c** was obtained in 48% yield as a single diastereomer.

With a viable route to compound **15c** in hand, a hydroxylative Knoevenagel reaction ($PhS(O)CH_2CN$, piperidine) was carried out to extend the carbon chain and introduce the α-hydroxyl group.[14] Instead of the corresponding alcohol, lactone **20** was obtained in good yield and with excellent diastereoselectivity (dr > 20:1, Scheme 4).[15] By taking advantage of the unique conformation of compound **20**, the C12−C13 double bond was selectively hydrogenated (10% Pd/C, H_2) to generate compound **21** in satisfactory yield.

At this point, we turned our attention to the construction of the final seven-membered ring through an intramolecular aldol condensation. Toward this end, compound **21** was partially reduced to aldehyde **3** and subjected to a variety of aldol conditions. Eventually, we found that aldehyde **3** participates in a base-mediated cyclization to afford (+)-allocyathin B_2 (**1**) in satisfactory yield (Scheme 4).[4a,16] The spectroscopic properties of synthetic (+)-allocyanthin B_2 were in full agreement with those reported in the literature.[4]

In conclusion, the first enantioselective synthesis of (+)-allocyathin B_2 was accomplished in 16 steps from 2-methylcyclopentanone highlighting a Pd-catalyzed enolate AAA reaction, a diastereoselective Ru-catalyzed cycloisomerization, and a unique hydroxylative Knoevenagel reaction. The unusual olefin isomerization in the Ru-catalyzed cycloisomerization was investigated and exploited for the synthesis. Since glycosidation of **1** produces erinacine A (**2**),[4c] this asymmetric route also constitutes a formal synthesis of this natural product as well. A full account of our efforts will be published in due course.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their generous support of our program. Mass spectra were provided by the Mass Spectrometry Facility, University of California, San Francisco, supported by the NIH Division of Research Resources. We are grateful to Prof. H. Kawagishi for sharing the NMR spectra of (+)-allocyathin B_2.

Supporting Information Available: Full experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0435586