Pergamon

Tetrahedron Letters, Vol. 37, No. 48, pp. 8787-8790, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02032-1

Exploitation of Palladium-Catalyzed Reductive Enyne Cyclization in the Synthesis of (–)-4a,5-Dihydrostreptazolin

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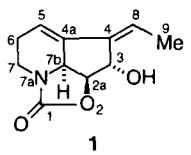
Abstract: Hydroxyl-promoted reductive cyclization of enyne compounds catalyzed by $Pd(OAc)_2$–BBEDA was explored and found to effect constructing the pyrindine framework with the alkylidene appendage. This methodology was applied to the stereoselective synthesis of (–)-4a,5-dihydrostreptazolin.

We have currently reported[1] the stereoselective synthesis of antibiotic (+)-streptazolin (**1**) utilizing a palladium-based approach for constructing the pyrindine core skeleton bearing the *Z* ethylidene group. This approach involves palladium-catalyzed enyne cycloisomerization which has broadly been developed by Trost.[2]



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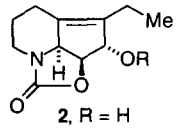
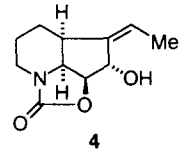


2, R = H
3, R = Ac



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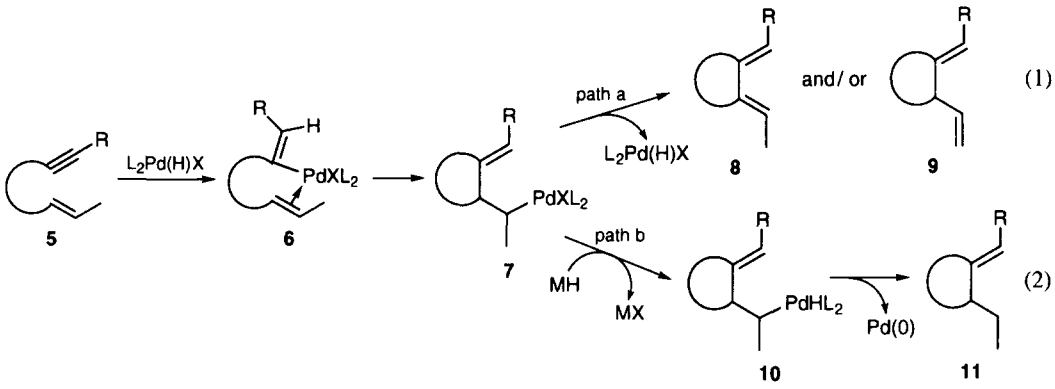
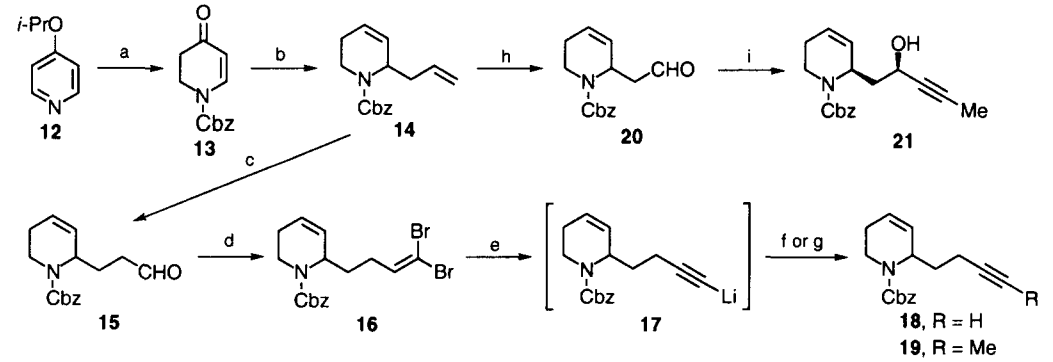
The mechanism of this catalytic reaction can be accounted for by a pathway invoking formation of a hydridopalladium(II) species, $L_2Pd(H)X$, followed by hydropalladation of the carbon–carbon triple bond to generate **6** with pentacoordinate Pd(II)[3] that initiates carbopalladation to form the cyclic intermediate **7**. Subsequent pathway involving β-elimination (path a) generates the 1,3- and/or 1,4-diene products (**8** and/or **9**) and regenerates the catalyst, $L_2Pd(H)X$ (eq 1). On the other hand, when the palladium-catalyzed reaction is carried out in the presence of an appropriate hydride source, hydride exchange (path b) followed by reductive elimination occurs to produce the exocyclic olefin **11**.[4]

While the nonreductive palladium-catalyzed enyne cyclization (eq 1) has extensively been studied,[2] relatively limited investigations of the reductive enyne cyclization (eq 2) and its synthetic use[5] have appeared. In this context, we became interested in developing an efficient protocol for the reductive palladium-catalyzed enyne cyclization applicable to the synthesis of 4a,5-dihydrostreptazolin (**4**), which was anticipated to exhibit enhanced stability in contrast to streptazolin (**1**) having a tendency to undergo polymerization in concentrated form due to the presence of the conjugated diene part. Additionally, we were intrigued by the potential of **4** as a therapeutic agent. These expectations were based on the fact that the acetate derivative **3** of 5,8-dihydrostreptazolin (**2**) has been recognized to be highly stable and found to exhibit marginal antibacterial and antifungal activity.[6]

To test the viability of this cyclization approach using the reductive cyclization methodology the racemic enyne compounds **18**, **19**, and **21** were first prepared as substrates as outlined in Scheme 1. The *N*-acyl dihydropyridone **13**, prepared[7] from 4-propoxypyridine (**12**), was converted to the 2-allyltetrahydropyridine **14** by reduction with $NaBH_4/CeCl_3$ followed by Lewis acid induced allylation.[8] The aldehyde **15** obtained via



hydroboration followed by catalytic TPAP oxidation[9] underwent dibromomethylenation to give **16**. Treatment of **16** with 2 equiv of BuLi resulted in *in situ* generation of the lithium acetylide **17**, which on acidic treatment or reaction with iodomethane provided the enynes with the terminal or inner acetylenes, **18** or **19**, respectively. On the other hand, the aldehyde **20** obtained by oxidative cleavage of the olefin in **14** was treated with the cerium(III) reagent, prepared from 1-propynyllithium and $CeCl_3$,[10] to afford a ca. 1:1 epimeric mixture of the alcohols, which was separated by column chromatography on silica gel (hexane–EtOAc, 10:1) to yield **21**.



Scheme 1: (a) CbzCl, $NaBH_4$, MeOH, −80 °C, then 1 N HCl (76%); (b) (i) $NaBH_4$, $CeCl_3$, MeOH, 0° C; (ii) CH_2=$CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, −80 °C (88%); (c) (i) 9-BBN, THF, then 3 N NaOH, 30% H_2O_2 (83%); (ii) Pr_4NRuO_4 (TPAP) (5 mol %), *N*-methylmorpholine *N*-oxide , CH_2Cl_2, rt (67%); (d) CBr_4, Ph_3P, CH_2Cl_2, rt (94%); (e) BuLi/hexane, THF, −80 °C; (f) to give **18**: 1 N HCl (85% from **16**); (g) to give **19**: MeI, HMPA (76% from **16**); (h) OsO_4–$NaIO_4$, dioxane–H_2O (52%); (i) MeC≡$CCeCl_2$, THF, −80 °C, then chromatographic separation of the alcohol epimers (25%).

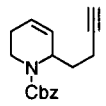
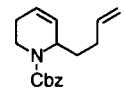
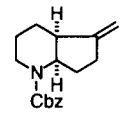
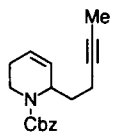
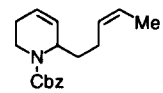
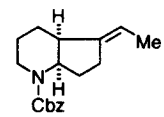
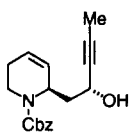
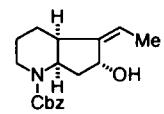
The enynes **18**, **19** and **21** were subjected to 5 mol % of $Pd(OAc)_2$ and 5 mol % of *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) in the presence of the hydride source in the appropriate solvent including 2 equiv of acetic acid (reflux) to afford the results shown in Table 1. Upon treatment of **18** in the presence of Bu_3SnH as a hydride source in benzene, chemoselective semihydrogenation of the acetylene[11] was observed to form the diene **22** (entry 1). When the reaction of **18** was carried out using hydride from polymethylhydrosiloxane (PMHS) instead of Bu_3SnH in benzene (reflux, 20 min), reductive cyclization smoothly proceeded to produce the pyrindine **23** in 78% yield (entry 2). In this case, when the same reaction was performed in the absence of acetic acid, however, **23** was formed only in 5% yield. These results obtained using PMHS are consistent with a mechanism discussed above for reductive cyclization according to path b (eq 2) which involves regeneration of the active catalyst, $L_2Pd(H)OAc$, by addition of acetic acid to Pd(0). In the

case of the reaction using Bu_3SnH as a hydride source (entry 1), in the competing process between hydride reduction of palladium (in **6**) and cyclization (**6** → **7**) the former process would predominate.

In marked contrast with the terminal acetylene **18**, the reaction of the internal acetylene **19** was found to be sluggish. Thus, upon prolonged heating of **19** in the presence of PMHS in benzene (reflux, 9 h), the reductive cyclization product **25** with pure *E* ethylidene stereochemistry was obtained in a low yield (26%) together with the semihydrogenation product **24** (48%) purely in *Z* form as a major product (entry 4). When this reaction was performed using PMHS in toluene (reflux, 7 h), reductive cyclization proceeded without the competitive formation of **24**, providing **25** in 58% yield along with 29% recovered starting material (entry 5). By using the same conditions as in entry 5 but replacing PMHS as a hydride donor with Ph_2SiH_2 **19** underwent exclusively semihydrogenation to yield **24** (entry 3).

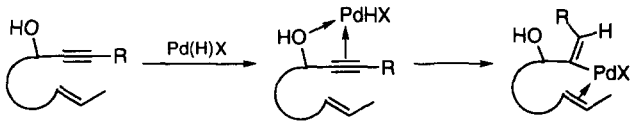
When a benzene solution of the propargyl alcohol **21** was treated under the same catalytic conditions as above for **19**, the rate of the cyclization reaction was dramatically improved; thus as shown in entry 6 the reaction was completed in 10 min ! instead of 9 h (benzene) or 7 h (toluene) with **19**, providing the pyrindine **26**. The fact that unusually rapid cyclization occurred, despite the expectation that the internal acetylene serves to be sluggish to cyclization as seen above, would be rationalized by eq 3 invoking precoordination between Pd

Table 1. Palladium-catalyzed reaction of the enynes **18**, **19**, and **21** in the presence of hydride reagents.[a]

Entry	Enyne	Hydride Reagent (Equiv[b])	Solvent	Time	Product (% Yield[c])
1	 **18**	Bu_3SnH (3)	benzene	2 h	 **22** (42)
2	**18**	PMHS (10)	benzene	20 min	 **23** (78)
3	 **19**	Ph_2SiH_2 (6)	toluene	12 h	 **24** (78)
4	**19**	PMHS (10)	benzene	9 h	**24** (48) +  **25** (26)
5	**19**	PMHS (10)	toluene	7 h	**25** (58)
6	 **21**	PMHS (10)	benzene	10 min	 **26** (50)

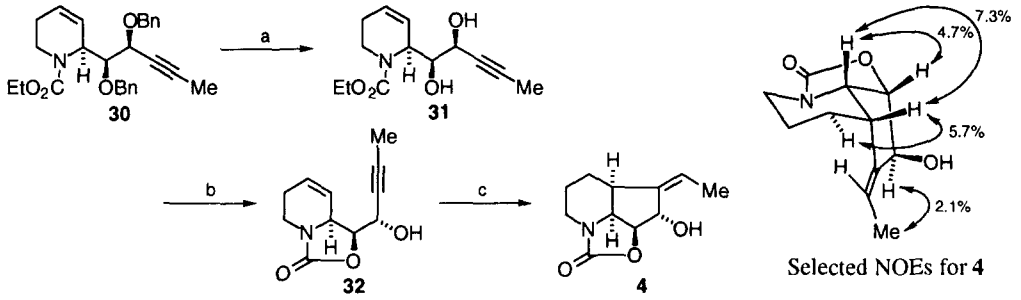
[a] All reactions were conducted with $Pd(OAc)_2$–BBEDA (5 mol %) in the presence of the hydride source in the appropriate solvent including AcOH (2 equiv) at reflux temperature. [b] Based on hydride ion. [c] Isolated yield after chromatographic purification.

and the hydroxyl group.[12] Such chelate formation (**28**) would facilitate subsequent hydropalladation to the internal acetylene to form **29** with excellent regiocontrol, wherein the Pd–C bond is positioned suitably for the following carbopalladation process to form ring as illustrated above in eqs 1 and 2 (**6** → **7**).



27 **28** **29** (3)

Having secured hydroxyl-promoted reductive cyclization to elaborate the pyrindine framework, we next turned to the synthesis of 4a,5-dihydrostreptazolin (**4**) utilizing the chiral enyne **30**, which we had described earlier,[1] as a precursor for reductive cyclization (Scheme 2). Selective removal of the benzyl protecting groups was conducted by exposure of **30** to BCl_3 at −10 °C to furnish the glycol **31** in 75% yield. Subsequent basic treatment of **31** resulted in the cyclic urethane **32** in 88% yield. The synthetic protocol used for the reductive cyclization of the propargyl alcohol **21** (Table 1, entry 6) was now successfully applied to **32**, which effected the stereoselective ring formation to afford in one step (−)-4a,5-dihydrostreptazolin (**4**), isolated as stable colorless needles, mp 154–155 °C (EtOAc–hexane); $[\alpha]^{23}_D$ −24.3 (*c* 0.54, $CHCl_3$), in 58% yield. The stereostructure and *Z* geometry of **4** were unambiguously assigned by ^1H NOE experiments.



Selected NOEs for **4**

Scheme 2: (a) BCl_3, CH_2Cl_2, −10 °C, 15 min (75%); (b) 20% KOH, *i*-PrOH, rt (88%); (c) $Pd(OAc)_2$–BBEDA(10 mol %), PMHS (10 equiv), AcOH (2 equiv), benzene, reflux, 30 min (58%).

Further works on biological evaluation of synthetic (−)-4a,5-dihydrostreptazolin (**4**) and extension of this reductive cyclization methodology to the stereoselective synthesis of natural alkaloids are underway.

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(*Received in Japan* 17 *September* 1996; *revised* 8 *October* 1996; *accepted* 14 *October* 1996)