Pergamon

Tetrahedron Letters 41 (2000) 4801–4804

TETRAHEDRON LETTERS

Stereocontrolled synthesis of (+)-lycoperdic acid based on a palladium catalyzed reaction using a serine-derived organozinc reagent

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Received 28 March 2000; revised 24 April 2000; accepted 28 April 2000

Abstract

An efficient stereocontrolled synthesis of (+)-lycoperdic acid has been achieved based on palladium catalyzed cross-coupling reaction of (*Z*)-1-(*tert*-butyldimethylsiloxy)-3-iodo-6-(*p*-methoxybenzyl)oxy-2-hexene with the organozinc reagent, prepared from *N*-Boc-β-iodoalanine methyl ester.

Keywords: amino acids; palladium catalyzed reactions; coupling reactions; organozinc compounds.

In connection with a project directed towards a total synthesis of dysiherbaine (**2**), a novel neuroexitotoxin occurring in a Micronesian marine sponge *Dysidea herbacea*,[1] we became interested in lycoperdic acid (**1**), a non-proteinogenic α-amino acid isolated from the mushroom *Lycoperdon perlatum* (Fig. 1).[2,3] This amino acid is the 5′-oxo analogue of 2-amino-3-(2′-carboxy-5′-tetrahydrofuranyl)propanoic acid which is the core structure of dysiherbaine (**2**). Although there has been no report concerning biological activity, lycoperdic acid (**1**) is expected to possess neuroexcitatory activity because of structural similarity with glutamic acid, a major neuroexcitatory substance in the mammalian central nerve system. This combination of structural features and potential biological activity prompted us to investigate a total synthesis of (+)-lycoperdic acid (**1**).

Our strategy leading to lycoperdic acid (**1**) relies on palladium catalyzed cross-coupling reaction of an alkenyl iodide or triflate **5** (X=I or OTf) with the organozinc reagent **4**, prepared from **3**, based on Jackson's method[4] originated from Tamaru's protocol[5] (Scheme 1). We envisaged that total synthesis of **1** would be achieved stereoselectively from the coupling product **6** through three major transformations; (i) diastereoselective epoxidation; (ii) acid catalyzed cyclization; (iii) oxidation.

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0040-4039/00/$ - see front matter
PII: S0040-4039(00)00719-X

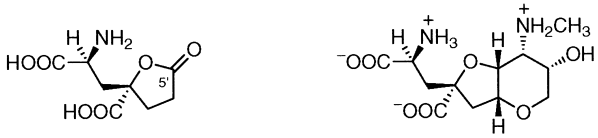
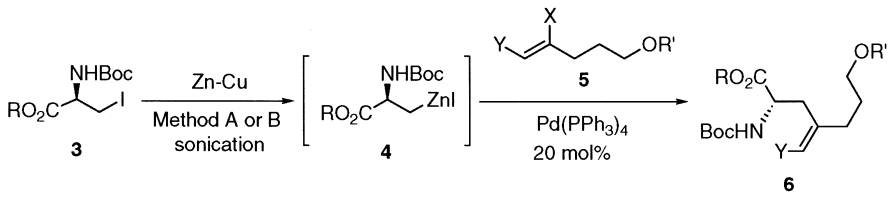


Figure 1.

Although various examples of the palladium catalyzed coupling reactions using organozinc reagents derived from L-serine have already been described in the literature,[4,6] aryl halides were predominantly used as a coupling partner and little attention has been paid to acyclic alkenyl halides or triflates. Therefore, we first undertook experiments summarized in Table 1. Coupling reactions of **5a–d** were carried out using 0.2 equivalents of $Pd(PPh_3)_4$ and organozinc reagent **4**, prepared in situ from 3 equivalents of **3** (R = Bn).† As can be seen from Table 1, this reaction was found to be applicable to both alkenyl iodides and triflates and the corresponding coupling products **6a–d** were obtained in moderate to excellent yields, except for the example listed in entry 3. In the case of the alkenyl triflate, addition of LiCl turned out to produce better results (entries 5 and 6).



Scheme 1.

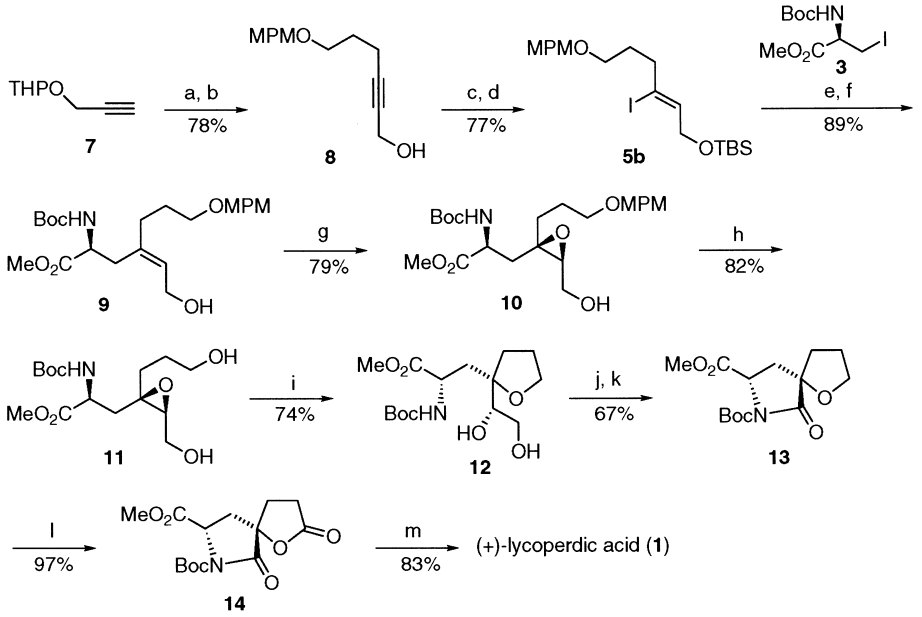
Table 1
Palladium catalyzed reactions of the organozinc reagent prepared from **3** (R = Bn) with **5**

entry	alkene **5** X	Y	R'	method[a]	solvent[b]	additive (eq.)	temp. (°C)	yield of **6a-d**[c] (%)
1	**5a**: I	CH_2OTHP	MPM	A	PhH-HMPA (10:1)	none	80	63
2	**5b**: I	CH_2OTBS	MPM	A	PhH-HMPA (10:1)	none	80	97
3	**5c**: I	CH_2OH	MPM	A	PhH-HMPA (10:1)	none	80	0
4	**5d**: OTf	H	TBDPS	A	PhH-HMPA (10:1)	none	80	46
5	**5d**: OTf	H	TBDPS	A	PhH-HMPA (10:1)	LiCl (3)	80	65
6	**5d**: OTf	H	TBDPS	B	THF	LiCl (4.5)	50	69

a) Method A: PhH-DMA (10 : 1), 45 °C, Method B: THF-DMA (10 : 1), 55 °C; b) same volume as that used for the preparation of the organozinc reagent; c) isolated yield. (DMA: *N,N*-dimethylacetamide)

† Since benzyl 2-(methoxycarbonylamino)acrylate was also formed under these conditions, the use of 3–5 equiv. of *N*-Boc-β-iodoalanine was required for sufficient production of the organozinc reagent.

Scheme 2 illustrates the synthesis of (+)-lycoperdic acid (**1**) based on the above-mentioned strategy. Alkylation of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (**7**) with 1-iodo-3-(*p*-methoxybenzyl)oxypropane, followed by removal of the THP ether protecting group gave propargyl alcohol **8**. Reaction of **8** with Red-Al®,[7] followed by treatment of the resulting alkenylaluminum complex with iodine allowed stereo- and regioselective formation of the corresponding (*Z*)-iodoalkene which was protected as its TBS ether to give **5b**.



Scheme 2. (a) *n*-BuLi, 1-iodo-3-(*p*-methoxybenzyl)oxypropane, THF–HMPA, –25°C to rt; (b) PPTS, MeOH, reflux; (c) $NaH_2Al(OCH_2CH_2OMe)_2$, Et_2O, then I_2; (d) *tert*-$BuMe_2SiCl$, Et_3N–DMAP, CH_2Cl_2; (e) **3** (2.5 equiv.), Zu–Cu (2.8 equiv.), benzene–DMA (10:1), sonication, 45°C, then **5b** in benzene–HMPA (5:2), $Pd(PPh_3)_4$ (5 mol%), 80°C; (f) AcOH–H_2O–THF (3:1:1); (g) diisopropyl L-tartrate (10 mol%), $Ti(O\text{-}i\text{-}Pr)_4$ (8 mol%), *t*-BuOOH (2 equiv.), 4A molecular sieves, CH_2Cl_2, –30°C; (h) DDQ, CH_2Cl_2–H_2O (20:1); (i) PPTS, CH_2Cl_2; (j) $Pb(OAc)_4$, THF, –20°C; (k) H_2CrO_4, acetone; (l) $RuCl_3$ (10 mol%), $NaIO_4$ (4 equiv.), CCl_4–MeCN–H_2O (2:2:3); (m) 6 M HCl, reflux

Upon reaction of **5b** with the organozinc reagent, prepared in situ from **3** (R = Me, see entry 2 in Table 1), palladium catalyzed coupling reaction took place very cleanly and, after desilylation, allylic alcohol **9**, $[\alpha]_D^{21}$ +2.9 (*c* 1.18, $CHCl_3$), was obtained in good yield. Katsuki–Sharpless catalytic asymmetric epoxidation[8] of **9** proceeded with complete diastereoselectivity to give epoxide **10**, $[\alpha]_D^{23}$ –4.6 (*c* 1.40, $CHCl_3$), which was then subjected to oxidative removal[9] of the MPM ether protecting group to afford diol **11**, $[\alpha]_D^{22}$ +2.8 (*c* 1.55, $CHCl_3$). Treatment of **11** with PPTS brought about stereoselective cyclization with complete inversion of stereochemistry at the quaternary center to give tetrahydrofuran **12** which was directly subjected to $Pb(OAc)_4$-oxidation and Jones oxidation to provide lactam **13**, $[\alpha]_D^{20}$ –44.6 (*c* 0.55, $CHCl_3$), in 50% overall yield. RuO_4-oxidation[10‡] of **13** gave known lactone **14**, mp 144–146°C, $[\alpha]_D^{27}$ –70.4 (*c* 1.05, $CHCl_3$) {lit.[3] mp 143–145°C, $[\alpha]_D^{21}$ –68.2 (*c* 1.10, $CHCl_3$)}, almost quantitatively. Finally, acidic hydrolysis of **14** according to the reported procedure[3] furnished (+)-lycoperdic acid (**1**), mp 200–202°C, $[\alpha]_D^{28}$ +12.7 (*c* 0.21, H_2O)

‡ RuO_4-oxidation of **12** gave **14** directly but in poor yield (20%).

{lit.[3] mp 200–201°C, $[\alpha]_D^{20}$ +14.9 (*c* 0.47, H_2O)}. The synthetic substance exhibited spectral properties (^1H and ^{13}C NMR) in accord with those reported.[3]

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