Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 345-348, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00009-7

Stereoselective Synthesis of Enantiopure β, γ-Disubstituted α-Alkylidene-γ-butyrolactones via A Palladium(II) Catalyzed Cyclization

Guoxin Zhu and Xiyan Lu*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032, China

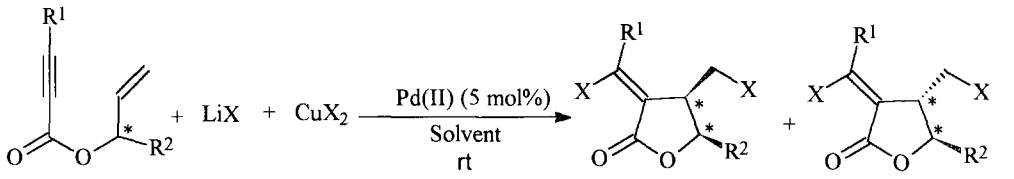
Abstract: β, γ-disubstituted α-alkylidene-γ-butyrolactones with *cis* or *trans* relative configurations were synthesized in both optically active forms from readily available homochiral allylic 2-alkynoates by Pd(II) catalysis in the presence of CuX_2 and LiX.

Synthesis of homochiral compounds as candidates for drug screening is becoming a key issue in the pharmaceutical industry.[1] Chiral, non-racemic γ-lactones are important synthetic intermediates in the syntheses of many natural products.[2] They are also key moieties in a wide range of natural products and biologically active compounds.[3] The physiological activity of these γ-lactones often depends on the absolute configuration.[4] Thus, a variety of synthetic methods for these compounds continues to be reported.[1-3, 5]

Transition metal catalyzed reactions, especially those that construct cyclic structures from easily available acyclic precursors, have received much attention owing to the template action of the transition metals.[6] Recently, we have developed some efficient methods for the construction of α-alkylidene-γ-butyrolactone ring from acyclic allylic 2-alkynoates under the catalysis of palladium(II).[7, 8] Our recent research revealed that when a stereogenic center was introduced into the 1'-position of the 2'-alkenyl group in the starting material, the reaction showed unusually high diastereoselectivity. In this communication, we wish to report this unusual stereochemistry and its application in the synthesis of enantiopure β, γ-disubstituted α-alkylidene-γ-butyrolactone derivatives.

We began our research with (R)-1'-pentylallyl 2-butynoate(**(R)-1a**) under $PdCl_2(PhCN)_2$ catalysis in the presence of $CuCl_2$ and LiCl in acetonitrile. The reaction went on cleanly, only *cis*-product (referring to the relative stereochemistry of 4, 5-substituents), **(4R, 5R)-2aA** was obtained in high yield (95%)(entry 1 in Table). The exocyclic C-C double bond in **(4R, 5R)-2aA** was assigned as the *Z* configuration by comparing the

Table. Cyclization of Allylic 2-Alkynoates[9] Catalyzed by Pd(II) in the Presence of CuX_2 and LiX



Entry	1 R^1	1 R^2	1 configuration	X	Time (h)	Method[a]	Yield (%)[b]	Products (*cis* : *trans*)[c]
1[d]	Me	C_5H_{11}	**(R)-1a**	Cl	69	A	95.0	(**2aA : 3aA** > 97 : 3)[e]
2	Me	C_5H_{11}	**(S)-1b**	Cl	69	A	94.0	(**2bA : 3bA** > 97 : 3)[e]
3	Me	C_5H_{11}	**(R)-1a**	Br	20	B	78.0	(**2aB : 3bB** > 97 : 3)[e]
4	Me	C_5H_{11}	**(S)-1b**	Br	22	B	75.0	(**2bB : 3bB** > 97 : 3)[e]
5	Me	Ph	**(S)-1c**	Cl	50	A	73.0	(**2cA : 3cA** > 97 : 3)[e]
6	Me	Ph	**(S)-1c**	Br	20	B	70.0	(**2cB : 3cB** > 97 : 3)[e]
7	Pr	C_5H_{11}	**(R)-1d**	Cl	68	A	80.0	(**2dA : 3dA** > 97 : 3)[e]
8	Pr	C_5H_{11}	**(R)-1d**	Br	20	B	71.0	(**2dB : 3dB** > 97 : 3)[e]
9	H	C_5H_{11}	**(R)-1e**	Br	24	B	78.0	(**2eB : 3eB** = 29 : 71)[f]
10	H	C_5H_{11}	**(S)-1f**	Br	22	B	80.0	(**2fB : 3fB** = 29 : 71)[f]
11	H	Me	**(±)-1g**	Cl	24	A	60.0	(**2gA : 3gA** = 39 : 61)[f]
12	H	i-Pr	**(±)-1h**	Cl	25	A	70.0	(**2hA : 3hA** < 3: 97)[f]

a: **Method A**: substrate : $CuCl_2$: LiCl : $PdCl_2(PhCN)_2$ = 1 : 3 : 6 : 0.05, using MeCN as the solvent; **method B**: substrate : $CuBr_2$: LiBr : $Pd(OAc)_2$ = 1 : 4 : 4 : 0.05, using HOAc as the solvent.

b. Isolated yield.

c. The ratio was determined by ^1H NMR spectra, all new compounds gave satisfactory spectroscopic (IR, ^1H NMR, MS) and microanalytical or high resolution MS data.

d: A **typical procedure** is as follows: To a solution of **(R)-1a** (195 mg, 1 mmol), $CuCl_2$ (400 mg, 3 mmol) and LiCl (260 mg, 6mmol) in MeCN (10 mL) was added $PdCl_2(PhCN)_2$ (20 mg, 0.05 mmol), the reaction was monitored by TLC (eluent: petroleum ether / ethyl acetate=10 / 3). After the reaction was complete, ether (80mL) was added, and the mixture was washed with water (3 × 5 mL) and dried ($MgSO_4$). Preparative TLC on silica gel (eluent: petroleum ether / ethyl acetate = 10 / 2) afforded the product **2aA**(250 mg, 95%).[10]

e: The configuration of the exocyclic double bond was ***Z***.

f: The configuration of the exocyclic double bond was ***E***.

chemical shift of the vinylic proton with its analogues[7]. The relative stereochemistry of 4, 5-substituents in (**4R, 5R**)-**2aA** was determined to be *cis* based on the appearance of the strong NOE correlation signal between H_4 and H_5 in its ^1H 2D NOESY spectra. This stereochemistry was also supported by comparing its ^1H NMR spectroscopic data with those of similar compounds.[8] When we used **(S)-1b** as the substrate, **(4S, 5S)-2bA** could also be obtained in high yield (entry 2 in Table).

Considering that a carbon-bromine bond is more suitable for further elaboration to other functionalities, LiBr was used instead of LiCl. The cyclization reaction occurred smoothly in HOAc with high *cis*-diastereoselectivity (entries 3, 4 in Table), but no desired cyclic products could be obtained in acetonitrile. Cyclization of a phenyl substituted substrate **(S)-1c** also afforded the *cis*-isomer **(4R, 5S)-2a** as the sole cyclic product (entries 5, 6 in Table) under similar conditions. Similar results were obtained for (R)-1'-pentylallyl 2-hexynoate (**(R)-1d**)(entries 7, 8 in Table).

Interestingly, when we extended this reaction to the unsubstituted propynoate **(R)-1e**, the cyclization reaction afforded a pair of diastereomers (**(4R, 5R)-2eB** and **(4S, 5R)-3eB)** with a ratio of 29 : 71. The exocyclic C-C double bonds in the products were believed to be in the *E* configuration by comparison of the chemical shift of vinylic proton with their analogues.[7] It was worth noting that the *trans*-(**4S, 5R)-3eB** was the major product in this case and the reaction showed *trans*-selectivity for the unsubstituted propynoate, which is quite different with the *cis*-selectivity in the case of substituted 2-alkynoates. The *trans*-selectivity for the unsubstituted 2-propynoates was controlled by the bulkiness of the substituent in 1'-position of the starting material. When the substituent becomes sterically more hindered, i.e. when $R^2 = {}^iPr$, the cyclization afforded the *trans* stereomer as the single product.(entry 11 in table).

Although the 1, 2-stereoinduction leading to *trans*-selectivity has been reported in organolanthanide-mediated[11] and Ziegler-Natta catalysts induced[12] cyclization of 1, 5-dienes and some other transition metal catalyzed cyclization,[13] the *cis*-selectivity of the cyclization of substituted 2-alkynoates and the dependence of the stereochemistry on the substituent on the C-C triple bond is uncommon. Thus, using this method, we can synthesize the β, γ-disubstituted γ-lactones with *cis* or *trans* relative configuration in both optically active forms, just starting from substituted or unsubstituted homochiral propynoates which were easily obtained from optically active allylic alcohols.

These results indicate that the substituent on the C-C triple bond plays an important role in the stereochemistry of the present reaction. The mechanistic rationale concerning such stereochemical results and the application of this method in the synthesis of natural products are underway in our group.

Acknowledgment: We thank the National Natural Science Foundation of China and Chinese Academy of Sciences for financial support.

References and notes:

1. Borman, S. *Chem. Eng. News* **1990**, *68*, 9.
2. Grieco, P. A.; *Synthesis* **1975**, 67; Hoffmann, H. M. R.; Rabe, J. *Angew. Chem, Int. Ed. Engl.* **1985**, *24*, 94; Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157; Nagao, Y.; Dai, W.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211 and refs cited therein; Rojo, J.; Oarcia, M.; Carretero, J. C. *Tetrahedron* **1993**, *49*, 9787; Murta, M. M.; de Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 2537; Cossy, J.; Ranaivosata, J. L.; Bellosta, V. *Tetrahedron Lett.* **1994**, *35*, 1205.
3. Ariza, J.; Font, J.; Ortuno, R. M. *Tetrahedron* **1990**, *46*, 1931; Koch, S. C.; Chamberlin, A. R. *J. Org. Chem.*,**1993**, *58*, 2725 and refs cited therein; Menges, M.; Bruckner, R. *Synlett* **1993**, 901; Ribbons, D. W.; Sutherland, A. G. *Tetrahedron* **1994**, *50*, 3587 and refs cited therein.
4. R. M. Silverstein in *Semiochemistry, Flavors and Pheromones; Proceeding ACS Symposium;* T. E. Acree, Ed.; W.de Gruyter and Co.; Berlin, **1985**; pp121.
5. Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.*, 1994, **59**, 365 and refs cited therein.
6. Nobels, A. F.; Graziani, M.; Hubert, A. J. "*Metal Promoted Selectivity in Organic Synthesis*", Kluwer Academy Publishers, Dordrecht, **1991**; Trost, B. M. *Pure & Appl. Chem.*, **1992**, *64*, 315; Negishi, E. *Pure & Appl. Chem.* **1992**, *64*, 323; Backvall, J. -E. *Pure & Appl. Chem.* **1992**, *64*, 429; Kishi, Y. *Pure & Appl. Chem.* **1992**, *64*, 343; Noyori, R. *J. Synth. Org. Chem. Japan*, **1992**, *50*, 113.
7. Ma, S.; Lu., X. *J. Chem. Soc. Chem. Commun.*, **1990**, 783.; Ma, S.; Lu, X. *J. Org. Chem.*, **1991**, *56*, 5120; Ma, S.; Lu, X. *J. Org. Chem.*, **1993**, *58*, 1245.; S. Ma and X. Lu *J. Organomet. Chem.*, **1993**, *447*, 305; G. Zhu, X. Lu and S. Ma *J. Chem. Research(M), 1993*, 2467.
8. Ma, S.; Zhu, G.; Lu, X. J. Org. Chem., 1993, 58, 3692.
9. The starting chiral esters were prepared by esterification of homochiral allyic alcohols promoted by DCC in the presence of DMAP according to the similar way reported in ref. 7. **(R)-1a**: $[\alpha]_D^{25}$ = -9.0 (C 1.3, $CHCl_3$); **(S)-1b**: $[\alpha]_D^{25}$ = +8.73 (C 1.3, $CHCl_3$); **(S)-1c**: $[\alpha]_D^{25}$ = -1.11 (C 1.6, $CHCl_3$); **(R)-1d**: $[\alpha]_D^{25}$ = -12.9 (C 1.2, $CHCl_3$); **(R)-1e**: $[\alpha]_D^{25}$ = -3.85 (C 1.0, $CHCl_3$); **(S)-1f**: $[\alpha]_D^{25}$ = +3.86 (C 1.0, $CHCl_3$).
10. **2aA:** $[\alpha]_D^{25}$ = +26.8 (C 1.33, $CHCl_3$); ^{1}H NMR($CDCl_3$, 300 M Hz) δ 4.37(dt, J_1 = 9.86 Hz, J_2 = 4.93 Hz, 1H), 3.75(m, 1H), 3.54-3.43(m, 2H), 2.40(s, 3H), 1.85-1.59(m, 4H), 1.43-1.34(m, 4H), 0.91(t, J = 6.64Hz, 3H); IR ν 2900,, 2840, 1740, 1660, 1470, 1160 cm^{-1}; MS 268(M^+(2^{37}Cl), 1.02), 266(M^+(^{37}Cl, ^{35}Cl), 4.75), 264(M^+(2^{35}Cl), 6.19), 231, 229, 197, 195, 193, 131, 129(100.00); Anal. Cacld for $C_{12}H_{18}Cl_2O_2$: C, 54.30; H, 6.84. Found: C, 54.32; H, 7.09. **2bA**: $[\alpha]_D^{25}$ = -26.0(C 1.33, $CHCl_3$); **2aB**: $[\alpha]_D^{25}$ = -7.28 (C 1.25, $CHCl_3$); **2bB**: $[\alpha]_D^{25}$ = +7.2 (C 1.20, $CHCl_3$); **2cA**: $[\alpha]_D^{25}$ = -92.2 (C 1.02, $CHCl_3$); **2cB**: $[\alpha]_D^{25}$ = +93.6 (C 1.0, $CHCl_3$); **2dA**: $[\alpha]_D^{25}$ = +38.8(C 1.0, $CHCl_3$); **2dB**: $[\alpha]_D^{25}$ = +10.8(C 1.52, $CHCl_3$).
11. Molander, G. A.; Hoberg, J. O. *J. Org. Chem.*, **1992**, *114*, 3123; Gagne, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Chem.* **1992**, *114*, 275; Piers, W. E.; Bercaw, J. E. *J. Am. Chem. Soc.* **1990**, *112*, 9406.
12. Rigollier, P.; Young, R.; Fowley, L. A.; Stille, J. R. *J. Am. Chem. Soc.* **1992**, *114*, 9441; Young, R.; Stille, J. R. *Organometallics* **1990**, *9*, 3022.
13. Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org, Chem.* **1992**, *57*, 1682; Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464; Shimada, S. ; Hashimoto, Y.; Sudo, A.; Hasegawa, M.; Saigo, K. *J. Org. Chem.* **1992**, *57*, 7126.

(*Received in Japan* 25 *November* 1994; *accepted* 5 *January* 1995)