Cyclization Reactions

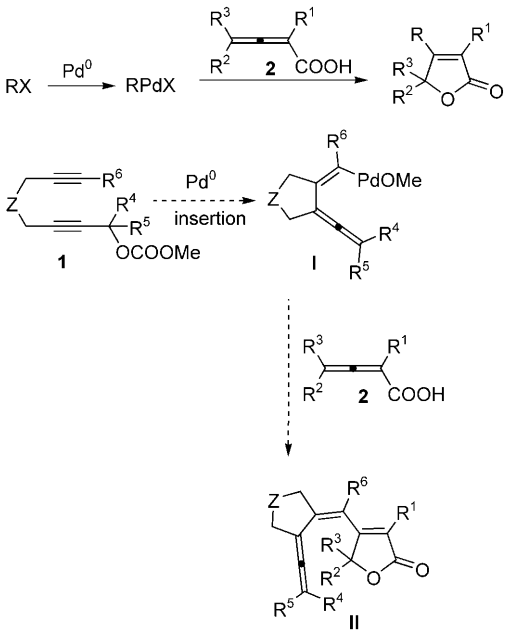
DOI: 10.1002/ange.200803424

An Efficient Approach to Substituted 1,5,7,8,9-Pentahydrocyclopenta-[*h*]-2-Benzopyran-3-one Derivatives by a Palladium-Catalyzed Tandem Reaction of 2,7-Alkadiynylic Carbonates with 2,3-Allenoic Acids**

*Xiongdong Lian and Shengming Ma**

Transition-metal-catalyzed cyclization reactions of functionalized allenes in the presence of organic halides have become powerful tools for the synthesis of cyclic compounds.[1–5] Based on this approach, we envisioned that a 1,3,4-trienyl palladium intermediate **I**, which is formed from the oxidative addition and cyclic carbopalladation of 2,7-alkadiynylic carbonates,[6] might act similarly to the aryl/alkenyl palladium intermediates formed from the oxidative addition of organic halides with palladium(0) to trigger the cyclization of 2,3-allenoic acids **2** to afford butenolides with a 1,3,4-trienyl unit at the β position (Scheme 1).[7] However, our preliminary study showed that the reaction of 2,7-alkadiynylic carbonate **1a** and 2,3-allenoic acid **2a** in the presence of $[Pd(PPh_3)_4]$ (5 mol%) in acetonitrile at 60°C for one hour failed to afford the **II**-type product. Instead, an interesting and unexpected new product was formed and isolated cleanly (Table 1, entry 1). The structure of this product was unambiguously established as the tricyclic product **3a** by X-ray diffraction analysis (Figure 1).[8] Herein, we report our recent observations in this area.

An assortment of palladium catalysts and solvents were screened for the transformation (Table 1). When $[Pd(PPh_3)_4]$ was used as the catalyst, the reaction proceeded smoothly in DMSO, DCE, and $MeNO_2$ (Table 1, entries 2–4). Among them $MeNO_2$ was shown to be the best solvent with **3a** isolated in 87% yield (Table 1, entry 4). Other solvents such as THF, DMF, *N*-methyl-2-pyrrolidone, and toluene, were ineffective (Table 1, entries 5–8). Whereas better results were not observed by using catalyst systems with $Pd(OAc)_2$/phosphrous-containing ligand (Table 1, entries 9 and 10). Bidentate ligands such as dppe and binap resulted in trace amount of product as determined by TLC analysis (Table 1, entries 11 and 12).



Scheme 1. Palladium(0)-catalyzed reaction of 2,3-allenoic acids with aryl or alkenyl halides (above) vs 2,7-alkadiynylic carbonates (below). X = halide, Z = tether.

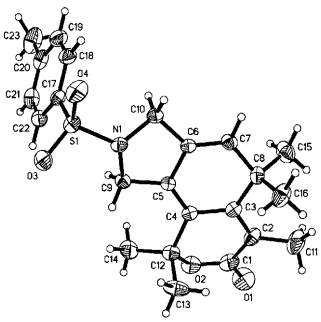


Figure 1. ORTEP plot of **3a** shown with ellipsoids at the 30% probability level.

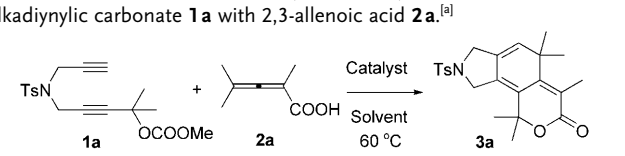
Next, the substrate scope of 2,3-allenoic acids **2** and 2,7-alkadiynylic carbonates **1** (which are N tethered) were surveyed under the optimized reaction conditions (Table 2, entries 1-9). Fully decorated 2,3-allenoic acids may be alkyl (Table 2, entry 1), allyl (Table 2, entry 2), or aryl (Table 2, entries 3 and 4) substituted. The carbon–carbon triple bond at the 7 position may be either terminal (Table 2, entries 1–8 and 11) or nonterminal (Table 2, entries 9 and 10). The reaction

[*] X. Lian, Prof. Dr. S. Ma
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032 (P.R. China)
Fax: (+86) 21-6416-7510
E-mail: masm@mail.sioc.ac.cn

[**] Financial support from the State Key Basic Research & Development Program (2006CB806105) and the National Natural Science Foundation of China (20732005) are greatly appreciated. We also thank J. Chen for reproducing the results presented in Table 2, entries 2 and 8, and Scheme 2.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803424.

Table 1: Effect of solvent and catalyst on the cyclization reaction of 2,7-alkadiynylic carbonate **1a** with 2,3-allenoic acid **2a**.[a]



Entry	Solvent	Catalyst	Yield [%][b] (%)[c]
1	MeCN	$[Pd(PPh_3)_4]$	100 (76)
2	DMSO	$[Pd(PPh_3)_4]$	100 (75)
3	DCE	$[Pd(PPh_3)_4]$	92
4	$MeNO_2$	$[Pd(PPh_3)_4]$	100 (87)
5	THF	$[Pd(PPh_3)_4]$	25
6	DMF	$[Pd(PPh_3)_4]$	42
7	NMP	$[Pd(PPh_3)_4]$	23
8	toluene	$[Pd(PPh_3)_4]$	11
9	$MeNO_2$	$Pd(OAc)_2$, 10 mol% tfp	100 (71)
10	$MeNO_2$	$Pd(OAc)_2$, 10 mol% Ph_3P	83 (66)
11	$MeNO_2$	$Pd(OAc)_2$, 5 mol% dppe	trace
12	$MeNO_2$	$Pd(OAc)_2$, 5 mol% binap	trace

[a] Under argon, a mixture of **1a** (0.3 mmol), **2a** (0.33 mmol), palladium complex (5 mol%), and ligand in solvent (3 mL) was stirred at 60°C for 1 h. [b] Determined by ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard. [c] Yield of isolated product. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, dppe = 1,2-bis(diphenylphosphino)ethane, NMP = *N*-methyl-2-pyrrolidone, tfp = tri(futan-2-yl)phosphine, Ts = 4-toluenesulfonyl.

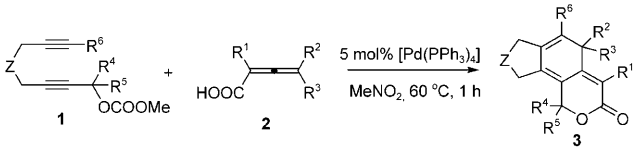
proceeded smoothly with primary (Table 2, entry 11), secondary (Table 2, entries 5 and 6), and tertiary (Table 2, entries 1–4 and 7–10) 2,7-diynylic carbonates. The method is also applicable to oxygen tethered (Table 2, entry 10) or carbon tethered (Table 2, entry 11) 2,7-alkadiynylic carbonates to form the corresponding tricyclic compounds **3j** and **3k**.

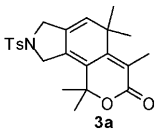
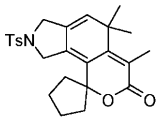
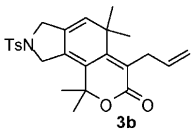
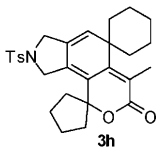
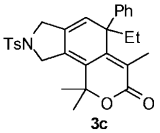
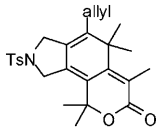
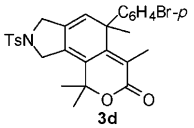
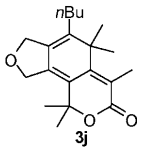
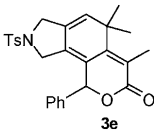
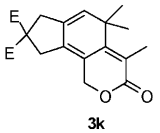
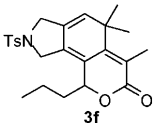
When optically active 2,7-diynylic tosylamide *R*-(+)-**1h**, which was prepared readily from propionaldehyde in four steps (Scheme 2, see the Supporting Information for experimental details),[9] was used, its cyclization with **2a** under the standard reaction conditions afforded the optically active product *R*-(−)-**3l** in 73% yield with greater than 99% *ee*.

In addition, it was observed that when 4-monosubstituted 2,3-allenoic acids **2f** and **2g** were used, the reaction yielded the aromatized tricyclic products **4** (Scheme 3). The structure of **4b** was also confirmed by X-ray diffraction analysis (Figure 2).[10]

A rationale is proposed for the above transformation (Scheme 4). Instead of triggering the normal cyclization to afford the expected product **II** (see Scheme 1), the carbon–carbon double bond at the 4 position of the 1,3,4-trienyl palladium species **I** would undergo highly regioselective intermolecular oxypalladation with 2,3-allenoic acid **2** to form an ester C–O bond to yield the palladabicyclic intermediate **III**. Regioselective intramolecular carbopalladation of the relatively electron-rich carbon–carbon double bond in the allenoic moiety in **III** would form the six-membered lactone ring and the seven-membered palladacycle. Subsequent reductive elimination of intermediate **IV** would form tricyclic product **3** and regenerate the catalytically

Table 2: Palladium-catalyzed cyclization reaction of 2,7-alkadiynylic carbonates **1** with 2,3-allenoic acids **2**.[a]



Entry	Products	Yield [%][b]	Entry	Products	Yield [%][b]
1	 **3a**	87	7	 **3g**	74
2	 **3b**	74	8	 **3h**	70
3	 **3c**	75	9	 **3i**	61
4	 **3d**	73	10	 **3j**	75
5	 **3e**	86	11	 **3k**	54
6	 **3f**	80			

[a] The reaction was carried out under argon in a Schlenk tube using **1** (0.3 mmol), **2** (0.33 mmol), and $[Pd(PPh_3)_4]$ (5 mol%) in $MeNO_2$ (3 mL) at 60°C for 1 h. [b] Yield of isolated product. E = COOEt.

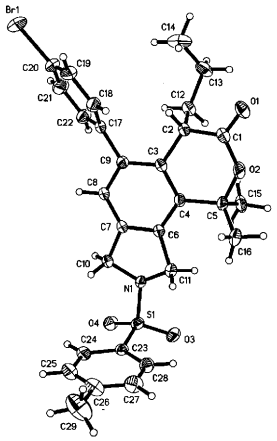
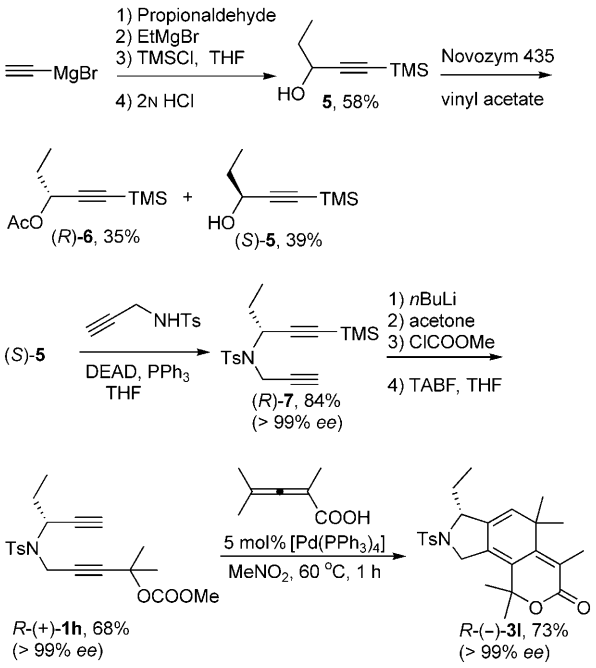
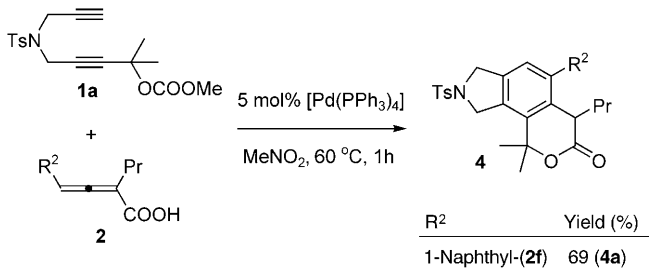


Figure 2. ORTEP plot of **4b** shown with ellipsoids at the 30% probability level.

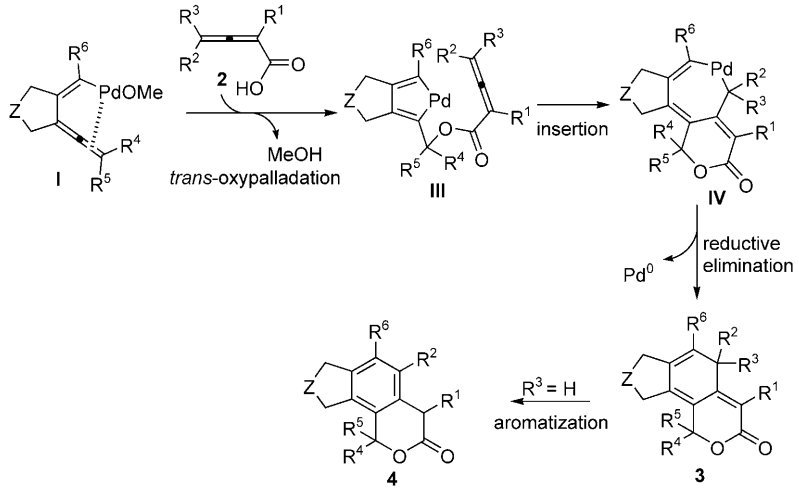


Scheme 2. Synthesis and cyclization of an optically active substrate. DEAD = diethyl azodicarboxylate, TBAF = *tetra-n*-butylammonium fluoride, TMS = trimethylsilyl.



R^2	Yield (%)
1-Naphthyl-(**2f**)	69 (**4a**)
4-BrC_6H_4-(**2g**)	59 (**4b**)

Scheme 3. Cyclization reaction of 2,7-alkadiynylic carbonate **1a** with 4-monosubstituted 2,3-allenoic acids **2**.



Scheme 4. A possible mechanism for the cyclization reaction of 2,7-alkadiynylic carbonates with 2,3-allenoic acids catalyzed by $[Pd(PPh_3)_4]$.

active palladium(0). For a 4-monosubstituted 2,3-allenoic acid, **3** may readily further aromatize to give the tricyclic **4** with a benzene ring in the center of the molecule.

In conclusion, we have developed an efficient methodology for the synthesis of 1,5,7,9-pentahydrocyclopenta[*h*]-2-benzopyran-3-one skeletons from easily available 2,3-allenoic acids[2b,c,11] and 2,7-alkadiynylic carbonates.[6b,c] Owing to the importance of this versatile skeleton,[12,13] the reaction will be potentially useful in organic synthesis and medicinal chemistry. Furthermore, the transformation revealed here involves the formation of four bonds within one synthetic operation.

Experimental Section

A typical procedure for the preparation of **3a**: 2,3-allenoic acid (**2a**, 42 mg, 0.33 mmol), $[Pd(PPh_3)_4]$ (17 mg, 0.015 mmol, 5 mol%), 2,7-alkadiynoic carbonate (**1a**, 110 mg, 0.3 mmol), and $MeNO_2$ (3 mL) were sequentially added to a dried and degassed Schlenk tube under Ar. The resulting reaction mixture was stirred at 60 °C for 1 h. When the reaction was complete (as evident by TLC), removal of the solvent by evaporation and purification by column chromatography on silica gel (eluent: CH_2Cl_2) afforded the pure **3a** (109 mg, 87%) as a colorless solid, m. p. 172–173 °C (acetone/diethyl ether 1:10). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.71$ (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 5.40 (s, 1H), 4.16 (s, 2H), 3.93 (s, 2H), 2.43 (s, 3H), 2.24 (s, 3H), 1.53 (s, 6H), 1.34 ppm (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 16.7$, 21.4, 26.6, 28.0, 38.6, 50.0, 52.3, 79.8, 122.8, 126.9, 127.6, 127.9, 129.8, 131.5, 132.2, 132.6, 144.1, 150.8, 165.4 ppm; EIMS: *m/z* (%): 413 (M^+, 15.07), 398 ($M^+ - CH_3$, 4.05), 91 (100); IR (thin film): $\tilde{\nu} = 1783$, 1698, 1597, 1347, 1163 cm^{-1}; elemental analysis calcd for $C_{23}H_{27}NO_4S$: C 66.80, H 6.58, N 3.39; found, C 66.78, H 6.47, N 3.31.

Received: July 15, 2008
Published online: September 24, 2008

Keywords: allenoic acids · cyclization · palladium · tandem reactions

[1] For reviews, see: a) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067; b) J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163; c) A. S. K. Hashmi, *Angew. Chem.* **2000**, *112*, 3737; *Angew. Chem. Int. Ed.* **2000**, *39*, 3590; d) R. W. Bates, V. Satchareon, *Chem. Soc. Rev.* **2002**, *31*, 12; e) L. K. Sydnes, *Chem. Rev.* **2003**, *103*, 1133; f) L. Brandsma, N. A. Nedolya, *Synthesis* **2004**, 735; g) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535; h) A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196; i) H.-U. Reissig, W. Schade, M. O. Amombo, R. Pulz, A. Hausherr, *Pure Appl. Chem.* **2002**, *74*, 175; j) S. Ma, *Pure Appl. Chem.* **2006**, *78*, 197; k) S. Ma, *Pure Appl. Chem.* **2007**, *79*, 261; l) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; m) S. Ma, *Aldrichimica Acta* **2007**, *40*, 91.

[2] a) S. Ma in *Topics in Organometallic Chemistry* (Ed.: J. Tsuji), Springer, Heidelberg, **2005**, pp. 183–210; b) *The Chemistry of the Allenes*, *Vol. 1* (Ed.: S. R. Landor), Academic Press, London, **1982**; c) *Modern Allene Chemistry*, *Vols. 1 and 2* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**; d) S.

Ma in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.Negishi), Wiley, New York, **2002**, pp. 1491 – 1521.

[3] For recent examples on the chemistry of allenes, see: a) J. Piera, A. Persson, X. Caldentey, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2007**, *129*, 14120; b) H. L. Shimp, G. C. Micalizio, *Chem. Commun.* **2007**, 4531; c) E. Skucas, J. F. Bower, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 12678; d) M. R. Luzung, P. Mauleon, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12402; e) H. E. Burks, S. B. Liu, J. P. Morken, *J. Am. Chem. Soc.* **2007**, *129*, 8766; f) A. R. Banaag, M. A. Tius, *J. Am. Chem. Soc.* **2007**, *129*, 5328; g) A. Barbero, P. Castreno, F. J. Pulido, *J. Am. Chem. Soc.* **2005**, *127*, 8022; h) K. M. Brummond, D. T. Chen, *Org. Lett.* **2005**, *7*, 3473; i) G. L. Hamilton, E. J. Kang, M. Mba, D. F. Toste, *Science* **2007**, *317*, 496; j) B. M. Trost, A. McClory, *Org. Lett.* **2006**, *8*, 3627; k) R. K. Dieter, N. Chen, V. K. Gore, *J. Org. Chem.* **2006**, *71*, 8755; l) N. Morita, N. Krause, *Eur. J. Org. Chem.* **2006**, 4634; m) A. S. K. Hashmi, M. C. Blanco, D. Fisher, J. W. Bats, *Eur. J. Org. Chem.* **2006**, 1387; n) C. J. T. Hyland, L. S. Hegedus, *J. Org. Chem.* **2006**, *71*, 8658; o) Z. Zhang, R. Widenhoefer, *Angew. Chem.* **2007**, *119*, 287; *Angew. Chem. Int. Ed.* **2007**, *46*, 283.

[4] For selected reports from our research group, see: a) F. Yu, X. Lian, S. Ma, *Org. Lett.* **2007**, *9*, 1703; b) Z. Gu, Y. Deng, W. Shu, S. Ma, *Adv. Synth. Catal.* **2007**, *349*, 1653; c) Z. Lu, G. Chai, S. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 14546; d) Z. Gu, X. Wang, W. Shu, S. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 10948; e) P. Lu, S. Ma, *Org. Lett.* **2007**, *9*, 5319; f) X. Jiang, X. Cheng, S. Ma, *Angew. Chem.* **2006**, *118*, 8177; *Angew. Chem. Int. Ed.* **2006**, *45*, 8009; g) S. Ma, L. Lu, *Chem. Asian J.* **2007**, *2*, 199; h) Y. Deng, Y. Yu, S. Ma, *J. Org. Chem.* **2008**, *73*, 585; i) X. Cheng, S. Ma, *Angew. Chem.* **2008**, *120*, 4657; *Angew. Chem. Int. Ed.* **2008**, *47*, 4581.

[5] For a palladium(II)-catalyzed cyclization of 2,3-allenoic acids in the presence of propargylic carbonates to afford β-allenyl butenolides, see: S. Ma, Z. Gu, Y. Deng, *Chem. Commun.* **2006**, 94.

[6] For the cyclic carbopalladation and coupling reaction of 2,7-alkadiynylic carbonates with typical organometallic reagents, see: a) J. Tsuji, T. Mandai, *Angew. Chem.* **1995**, *107*, 2830; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2589; b) W. Oppolzer, A. Pimm, B. Stammen, W. E. Hume, *Helv. Chim. Acta* **1997**, *80*, 623; c) R. Grigg, R. Rasul, V. Savic, *Tetrahedron Lett.* **1997**, *38*, 1825; d) F. Wang, X. Tong, J. Cheng, Z. Zhang, *Chem. Eur. J.* **2004**, *10*, 5338.

[7] a) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701; b) S. Ma, Z. Shi, *Chem. Commun.* **2002**, 540; c) S. Ma, Z. Shi, *J. Org. Chem.* **1998**, *63*, 6387.

[8] Crystal data for **3a**: Recrystallization from acetone/diethyl ether (1:10), $C_{23}H_{27}NO_4S$, MW = 413.52, Monoclinic, space group *P*21/*c*, Mo_K, final *R* indices [$I > 2\sigma(I)$], $R1 = 0.0633$, $wR2 = 0.1486$, *R* indices (all data): $R1 = 0.0963$, $wR2 = 0.1647$; $a = 12.6156(17)$ Å, $b = 7.5890(11)$ Å, $c = 23.006(3)$ Å, $\alpha = 90$, $\beta = 100.518(3)$, $\gamma = 90°$, $V = 2165.6(5)$ Å^3, $T = 293(2)$ K, wavelength: 0.71073 Å, $Z = 4$, reflections collected/unique 12125/4704 ($R_{int} = 0.1281$), number of observation [$I > 2\sigma(I)$] 2980, parameters 268. CCDC 675814 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] For reports of the kinetic resolution of propargylic alcohols, see: a) P. Allevi, P. Ciuffreda, M. Anastasia, *Tetrahedron: Asymmetry* **1997**, *8* 93; b) D. Xu, Z. Li, S. Ma, *Tetrahedron Lett.* **2003**, *44*, 6343.

[10] Crystal data for **4b**: Recrystallization from acetone/diethyl ether (1:10), $C_{29}H_{30}BrNO_4S$, MW = 568.51, Monoclinic, space group *P*21/*n*, Mo_K, final *R* indices [$I > 2\sigma(I)$], $R1 = 0.0424$, $wR2 = 0.0778$, *R* indices (all data): $R1 = 0.0984$, $wR2 = 0.0868$; $a = 17.4190(17)$ Å, $b = 9.6103(10)$ Å, $c = 31.794(3)$ Å, $\alpha = 90°$, $\beta = 93.815(2)°$, $\gamma = 90°$, $V = 5310.5(9)$ Å^3, $T = 293(2)$ K, wavelength: 0.71073 Å, $Z = 8$, reflections collected/unique 27183/9845 ($R_{int} = 0.0900$), number of observation [$I > 2\sigma(I)$] 4485, parameters 657. CCDC 675815 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] a) H. J. Bestmann, H. Hartung, *Chem. Ber.* **1966**, *99*, 1198; b) A. D. Abell, D. A. Hoult, K. M. Morris, J. M. Taylor, J. O. Trent, *J. Org. Chem.* **1993**, *58*, 1531; c) J.-E. Kang, E.-S. Lee, S.-I. Park, S. Shin, *Tetrahedron Lett.* **2005**, *46*, 7431; d) J. A. Marshall, M. A. Wolf, E. M. Wallace, *J. Org. Chem.* **1997**, *62*, 367; e) S. Ma, S. Wu, *J. Org. Chem.* **1999**, *64*, 9314; f) S. Ma, S. Wu, *Chem. Commun.* **2001**, 441.

[12] a) D. Nicoletti, A. A. Ghini, R. Furtmüller, W. Sieghart, R. H. Dodd, G. Burton, *Steroids* **2000**, *65*, 349; b) T. L. Jacobs, R. B. Brownfield, *J. Am. Chem. Soc.* **1960**, *82*, 4033; c) W. N. Speckamp, H. Kesselaar, *Tetrahedron Lett.* **1974**, *15*, 3405; d) Y. G. Lee, Y. Utsumi, K. Ohkata, K. Y. Akiba, *Heterocycles* **1990**, *30*, 813.

[13] A. W. Nicholas, M. C. Wani, G. Manikumar, M. E. Wall, K. W. Kohn, Y. Pommier, *J. Med. Chem.* **1990**, *33*, 972.

