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A Practical Synthesis of *Trans*-3-Substituted Proline Derivatives through 1,4-Addition

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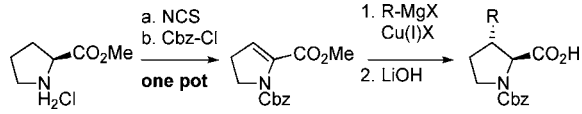
ABSTRACT



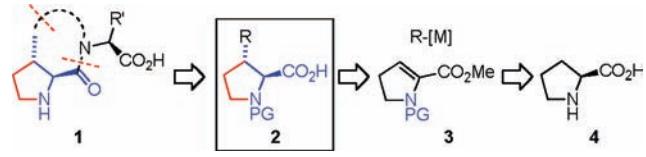
A practical four-step synthesis of 3-alkyl-, vinyl-, and aryl-substituted proline derivatives, which are important building blocks for conformationally restrained peptide analogs, was developed. The method relies on a Cu-catalyzed 1,4-addition of Grignard reagents to *N*-protected 2,3-dehydroproline esters, efficiently prepared in a new one-pot protocol. The 1,4-addition products are obtained with good *trans*-selectivity (*dr* 5:1 to 25:1). A nonracemic sample of *N*-Cbz-3-vinylproline (74% *ee*) was obtained using Evans oxazolidinone as a chiral auxiliary.

Trans-3-substituted proline derivatives of type **2** (Scheme 1) are widely used in the synthesis of conformationally constrained peptide mimetics (e.g., of type **1**),[1,2] as modified amino acid building blocks in peptide synthesis[3] and as intermediates in the synthesis of alkaloids.[4] The pharmacological relevance of such compounds was demonstrated in the development of potent hepatitis C virus protease inhibitors[3a] and farnesyl transferase inhibitors.[5]

So far, two approaches have mainly been used for the synthesis of compounds of type **2**: (1) *Michael*-addition of an amino-malonate to an α,β-unsaturated aldehyde with subsequent reduction and decarboxylation affords the *N*-protected products as racemates (*trans*/*cis* = ca. 2:1) in six steps in up to 40% overall yield but is not suitable for the synthesis of 3-vinyl-proline derivatives.[6,7] (2) An alternative method, introduced by *Herdeis*, utilizes a Cu-mediated 1,4-addition to α,β-unsaturated pyroglutamic acid derivatives followed by deoxygenation.[3a,4] This strategy provides the products in high stereochemical purity; however, it requires 10−11 steps and, accordingly, proceeds only with low overall yield.[8]

In the course of our research program aiming at the development of Pro-Pro dipeptide mimetics locked in a PPII-helix conformation,[1,9] we initially applied a (modified) *Herdeis* sequence for the synthesis of *trans*-3-vinyl-proline (**2**, PG = Boc, R = vinyl).[1] However, the large number of steps and the low overall yield prompted us to search for a

Scheme 1. A Strategy for the Synthesis of 3-Substituted Proline Derivatives (**2**) through 1,4-Addition



(1) Zaminer, J.; Brockmann, C.; Huy, P.; Opitz, R.; Reuter, C.; Beyermann, M.; Freund, C.; Müller, M.; Oschkinat, H.; Kühne, R.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2010**, *49*, 7111–7115.

(2) (a) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1679–l682. (b) Einsiedel, J.; Lanig, H.; Waibel, R.; Gmeiner, P. *J. Org. Chem.* **2007**, *72*, 9102–9113.

(3) (a) Perni, R. B.; et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1939–1942. (b) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1931–1938. (c) Jackson, D. Y.; Quan, C.; Artis, D. R.; Rawson, T.; Blackburn, B.; Struble, M.; Fitzgerald, G.; Chan, K.; Mullins, S.; Burnier, J. P.; Fairbrother, W. J.; Clark, K.; Berisini, M.; Chui, H.; Renz, M.; Jones, S.; Fong, S. *J. Med. Chem.* **1997**, *40*, 3359–3368.

(4) Hereides, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry* **1994**, *5*, 351–354.

(5) Latest example: DeSolms, S. J. U.S. Patent 5,872,135, 1999; CAN 130:196955.

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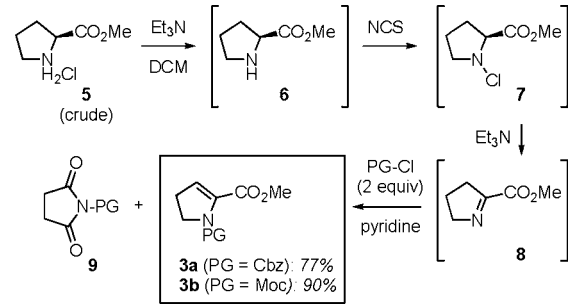
more practical alternative. Herein, we report an efficient, flexible, and operationally reliable four-step synthesis of *trans*-3-substituted prolines of type **2** following the strategy shown in Scheme 1.

Our concept is based on the consideration that the substituent R could be introduced to a *N*-protected 2,3-dehydroproline ester of type **3** by means of a Cu-catalyzed 1,4-addition. The *trans*-configuration should result from a diastereoselective protonation of the initially formed enolate.[10] As a precondition for the overall success, an efficient access to the required 2,3-dehydroprolines of type **3** from proline (**4**) is required. In principle, this method also allows the preparation of nonracemic compounds by either employing a chirally modified substrate or by performing the 1,4-addition in a catalytic enantioselective fashion.[11]

Initially, we synthesized the dehydroprolines **3a**/**b** according to the most common literature protocol. Thus, esterification of **4** (MeOH, $SOCl_2$, 100%)[12] and workup of the crude hydrochloride **5** with NEt_3 in ether gave rise to the methyl ester **6** in 75% yield after distillation. Oxidation of **6** with *t*BuOCl[13] with concomitant elimination of HCl according to *Häusler*[14a] then afforded the 1,2-dehydroproline **8** in 81% yield, again after distillation. Finally, treatment of **8** with Cbz-Cl or Moc-Cl in the presence of pyridine in CH_2Cl_2 delivered the 2,3-dehydroprolines **3a/b** in typical yields of 50 to 70%.[12b,c] However, despite reasonable high overall yields from proline (30% for **3a**, and 54% for **3b**) the method did not satisfy our demands for practicability.

Fortunately, we succeeded in developing a greatly improved one-pot procedure (see below), which allows direct conversion of the crude hydrochloride **5**, obtained in quantitative yield from **4** (see above), into the dehydroprolines **3a/b** in an efficient and reliable fashion on a 50 g scale (Scheme 2).

Scheme 2. One-Pot Synthesis of **3a/b** (Moc = Methoxy Carbonyl)



As a major change, we replaced the light-sensitive and dangerous *t*BuOCl by inexpensive NCS.[15] Due to its lower oxidation power this reagent allowed us to perform the reaction in the presence of NEt_3, which is a sufficiently strong base to directly induce HCl elimination (**7** to **8**). For this purpose, the crude hydrochloride **5** was dissolved in CH_2Cl_2 and treated with NEt_3 (2 equiv) prior to the portionwise addition of NCS. The resulting imine **8** was then converted to the *N*-protected enamine (**3a**/**3b**) simply by addition of Moc-Cl (or Cbz-Cl, respectively) and pyridine.[16] It proved to be crucial to use a 2-fold excess of both the chloroformiate (PG-Cl) and the base (pyridine) because the succinimide (formed from NCS) also consumes 1 equiv of the chloroformiate to give **9**.[17] In comparison to the literature method[14] our one-pot protocol (Scheme 2) affords the dehydroprolines **3a/b** in greatly improved overall yield from proline (77% of **3a**, 90% of **3b** after chromatography) and could be performed in the air using technical-grade solvents and reagents.[18]

Having developed a comfortable access to the dehydroprolines **3a/b**, we next investigated the Cu-catalyzed 1,4-addition of Grignard reagents to these compounds. Following an established protocol[19] we treated **3a** with 1.5 equiv of vinyl-MgBr in the presence of 0.3 equiv of $CuBr{\cdot}SMe_2$ at −30 °C in THF. Under these conditions the product *rac*-

(6) (a) Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.* **1990**, *55*, 270−275. Further examples: ref 3b−c.

(7) Recent variants of this method exploit an organocatalytic key step: (a) Rios, H. R.; Ibrahem, I.; Vesely, J.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 8695–8699. (b) Merck & Co., Emerson, K. M.; Ho, G.-J. *Chem. Abstr.* **2000**, *134*, 86538.

(8) For other syntheses of compounds of type **2**, see: (a) Soloshonok, V. A.; Ueki, H.; Tiwari, R.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2004**, *69*, 4984–4990. (b) Kanemasa, S.; Tatsukawa, A.; Wada, E. *J. Org. Chem.* **1991**, *56*, 2875–2874. (c) Damour, D.; Pulicani, J.-P.; Vuilhorgne, M.; Mignani, S. *Synlett* **1999**, 786–788.

(9) (a) Ball, L.; Kühne, R.; Schneider-Mergner, J.; Oschkinat, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 2852–2869. (b) Freund, C.; Schmalz, H.-G.; Sticht, J.; Kühne, R. *Handb. Exp. Pharmacol.* **2008**, *186*, 407–429.

(10) For noncatalytic 1,4-additions to substituted dehydroprolines, see: (a) Ezquerra, J.; Escribano, A.; Rubio, A.; Remuifiin, M. J.; Vaquero, J. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2613–2626. (b) Toyooka, N.; Okumura, M.; Himiyama, T.; Nakazawa, A.; Nemoto, H. *Synlett* **2003**, 55–58.

(11) Reviews: (a) Schmalz, H.-G. In *Comprehensive Organic Synthesis*, Vol. 4; Trost, M., Fleming, I., Eds.; Pergamon: Oxford, 1991; pp 199−236. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 711–806. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pamies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (d) Lopez, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179–188. For a recent contribution from this laboratory, see: (e) Robert, T.; Velder, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7718–7721.

(12) (a) Webb, R. G.; Haskell, M. W.; Stammer, C. H. *J. Org. Chem.* **1969**, *34*, 576–580. (b) Guttmann, S. *Helv. Chim. Acta* **1961**, *85*, 721–744.

(13) Peparation: Mintz, M. J.; Walling, C. *Org. Synth.* **1969**, *49*, 9–12.

(14) (a) Häusler, J. *Liebigs Ann. Chem.* **1981**, 1073–1088. (b) Shin, C.; Takahashi, N.; Yonezawa, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2020–2023. (c) Purvis, M. B.; LeFevre, J. W.; Jones, V. L.; Kingston, D. G. I.; Biot, A. M.; Gossolé, F. *J. Am. Chem. Soc.* **1989**, *111*, 5931–5935.

(15) For the NCS-oxidation of amines to *N*-chloroamines, see: (a) Furneaux, R. H.; Limberg, G.; Tyler, P. C.; Schramm, V. L. *Tetrahedron* **1997**, *53*, 2915–2930. (b) Haeberli, A.; Leumann, C. J. *Org. Lett.* **2001**, *3*, 489–492.

(16) Neither NEt_3 nor pyridine could be replaced by each other. Pyridine proved not to be basic enough to induce HCl elimination (**7** to **8**) while we assume pyridine to act as a catalyst in the acylation of **8**.

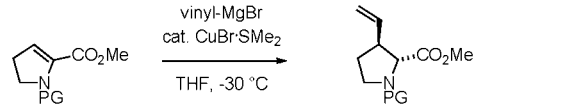
(17) With 1.5 equiv of Cbz-Cl/pyridine the yield of **3a** dropped to 30%.

(18) For other (operationally less attractive) entries to dehydroproline analogs of type **3** involving the oxidation of *N*-protected proline esters, see ref 10a (LiHMDS, PhSeCl) or Kublitskii, V. S.; Stepanov, A. E.; Trukhan, V. M. *Russian J. Org. Chem.* **2008**, *44*, 933–934 (LiHMDS, Br_2).

(19) Quinkert, G.; Schmalz, H.-G.; Walzer, E.; Gross, S.; Kowa1czyk-Przewloka, T.; Schierloh, C.; Dürner, G.; Bats, J. W.; Kessler, H. *Liebigs. Ann. Chem.* **1988**, 283–315.

10a was formed in 66% isolated yield as a (inseparable) 10:1 mixture of the *trans*- and *cis*-diastereomers (Scheme 3).[20]

Scheme 3. Cu-Catalyzed 1,4-Addition of Vinyl-MgBr to **3a/b**



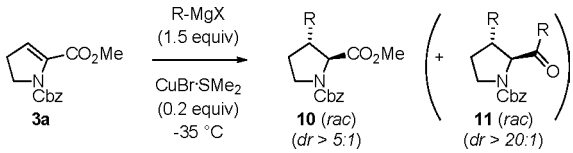
3a (PG = Cbz)
3b (PG = Moc)

10a (*rac*): 66% (*trans*:*cis* = *10:1*)
10b (*rac*): 52% (*trans*:*cis* = *6:1*)

In a similar experiment, the Moc-protected substrate **3b** afforded *rac*-**10b** in a slightly lower yield (52%; *trans*/*cis* = 6:1).

In the course of extensive experimentation it became obvious that a slow addition (by means of a syringe pump) of a solution of the substrate (**3**) to the Grignard/Cu(I) mixture is essential to ensure reproducible yields. A further improvement was achieved by changing the temperature of the initial cuprate formation from −10 to −35 °C and by lowering the amount of the Cu(I) catalyst to 15−20 mol %. Under the optimized conditions the product *rac*-**10a** was obtained in 80% yield, even on a 20 g (75 mmol) scale (Table 1). The generality of the protocol was demonstrated by also

Table 1. 1,4-Addition of Different Grignard Reagents to **3a**



entry	R−MgX	product (isol. yield)	dr^{20} (*trans*/*cis*)	byproduct (isol. yield)
1	Vinyl−MgCl	**10a** (80%)	11:1	–
2	Me−MgBr	**10c** (53%)	7:1	**11c** (13%)
3	*i*Pr−MgCl	**10d** (55%)	25:1	**11d** (11%)
4	Ph−MgBr	**10e** (59%)	5:1	**11e** (8%)

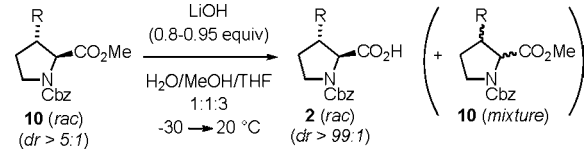
employing other Grignard reagents (Me, *i*Pr, and Ph) to give the products of type *rac*-**10** in 53−59% yield. Not unexpected, the product (*rac*-**10d**) with the most bulky substituent R was formed with the highest diastereoselectivity (*trans*/*cis* = 25:1).

As byproduct of the 1,4-addition, ketones of type *rac*-**11** were formed (notably as virtually pure diastereomers). Interestingly, such a byproduct was not observed in the synthesis of the vinyl derivative *rac*-**10a** (and *rac*-**10b**). We suppose that the ketones of type **11** arise from an initial attack of the Grignard reagent at the ester function of **3a** and Cu-catalyzed 1,4-addition to the resulting ketone (as the more reactive Michael acceptor).

(20) Due to signal overlap in the crude product, the *trans*/*cis* ratio was determined by means of ^{1}H NMR of the purified sample.

To further convert the 1,4-addition products (of type **10**) into the deprotected target compounds of type **2** (Scheme 1) the methylester function had to be saponified. Treatment of *rac*-**10a** with an excess of LiOH in H_2O/MeOH/THF[21] afforded *rac*-**2a** as a mixture of diastereomers in 87% yield. While initial attempts to achieve a selective hydrolysis of the sterically less hindered *trans*-diastereomer using NaOH in H_2O/MeOH[22] were not successful, we succeeded in achieving an efficient kinetic discrimination of the diastereomers by using less than 1 equiv of LiOH (0.8 to 0.95 equiv in H_2O/MeOH) and running the reactions at low temperature (slowly warming from −30 to 20 °C). In all four cases investigated (Table 2), the acids *rac*-**2** were isolated in good

Table 2. *Trans*-Selective Saponification of **10**



entry	R	substrate(*dr*)	product(yield)	*dr* ≥
1	vinyl	**10a** (11:1)	**2a** (74%)	99:1
2	Me	**10c** (7:1)	**2c** (71%)	99:1
3	*i*Pr	**10d** (25:1)	**2d** (69%)	99:1
4	Ph	**10e** (5:1)	**2e** (69%)	99:1

yield as analytically pure *trans*-diastereomers (*dr* ≥ 99:1) after extractive workup and without the need for additional purification.[23] The synthesis of the (yet racemic) compounds of type **2** was thus achieved in only four steps (29−46% overall yield) from **4**.

The *trans*-configuration of the acids of type *rac*-**2** was assigned by NOE-NMR spectroscopy (see Supporting Information) and additionally secured by an X-ray crystal structure analysis of *rac*-**2d** and **2f** (Figure 1).

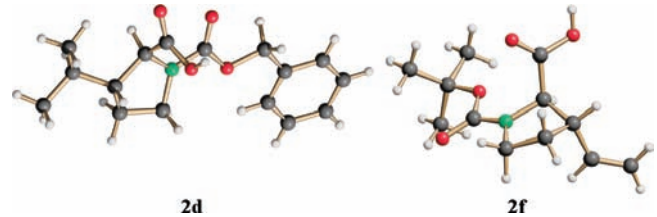


Figure 1. Structures of **2d** and **2f** in the crystalline state.

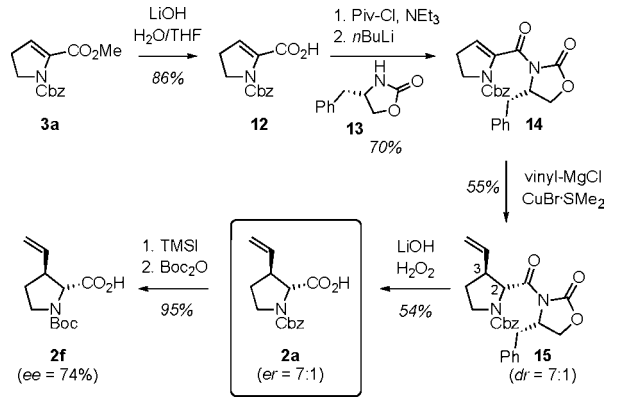
To exploit the developed method also for the synthesis of nonracemic compounds, we decided to probe the 1,4-addition

(21) Boger, D. L.; Yohannes, D.; Zhou, J.; Patane, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 3420–3430.

(22) Not unexpected, the diastereomers could not be separated by column chromatography; see ref 6 and Sarges, R.; Tretter, J. R. *J. Org. Chem.* **1974**, *39*, 1710–1716.

using a chirally modified dehydroproline derivative as a substrate. For this purpose compound **14** was prepared from **3a** by ester hydrolysis and subsequent coupling[24] of the acid **12** with Evans oxazolidinone **13**[25] (Scheme 4). Under the

Scheme 4. Synthesis of Nonracemic 3-Vinyl-proline Derivatives through Diastereoselective 1,4-Addition (Piv = Pivaloyl)

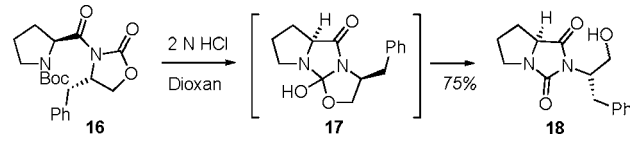


proven conditions, the key 1,4-addition then proceeded smoothly to give **15** with a useful degree of diastereoselectivity (*dr* = 7:1).[26,27]

After cleaving off the chiral auxiliary ($LiOH/H_2O_2$)[28] the *trans*-vinyl-proline derivative **2a** was isolated in 54% yield, supposably as a 7:1 mixture of enantiomers.[29] To determine the absolute configuration of the major enantiomer, the Cbz-group was replaced by Boc through treating **2a** with TMSI[30] and subsequently with Boc_2O (Scheme 4). The comparison of the optical rotation of the resulting compound **2f** ($[\alpha]_{589}$ = +28.3; $[\alpha]_{546}$ = +33.9; *c* = 1.125 in $CHCl_3$) with literature values[1] clearly indicated that the (2*R*,3*S*)-enantiomer of **2f** was formed with an enantiomeric excess of 74% *ee*. Within the experimental limits, this perfectly matched the value predicted from the *dr* (7:1) determined by ^{1}H NMR at the stage of **15**.

An interesting observation was made when we tried to optimize the access to the dehydroproline **14**. In an attempt to deprotect the chiral proline derivative **16** by treatment with 2 N HCl in dioxane[31] (in order to prepare for its oxidation to **14**) we isolated the novel hydantoine **18** in 75% yield (Scheme 5).

Scheme 5. Unexpected Formation of the Hydantoine **18**



The structure of **18** was proven through X-ray crystal structure analysis (Figure 2). We assume that after Boc-

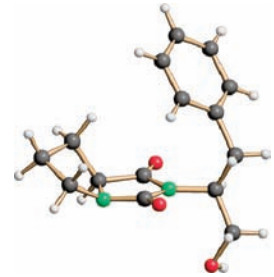


Figure 2. Structure of hydantoine **18** in the crystalline state.

cleavage the pyrrolidine nitrogen attacks the carbamate carbon atom to give intermediate **17**, from which **18** is readily generated as the more stable isomer. The formation of the hydantoine **18** was also observed even under neutral conditions (65% yield), i.e. on hydrogenolytic deprotection of the Cbz-protected analog of **16** (H_2, Pd/C, MeOH or EtOAc).

In conclusion we have developed a short and practical synthesis of *trans*-3-substituted proline derivatives (*rac*-**2**) allowing a late and flexible introduction of the substituent R. The dehydroproline derivatives (**3**) used as substrates for the Cu-catalyzed key step were efficiently prepared in a new one-pot protocol. While the nonracemic vinyl-proline **2a** was obtained with 74% *ee* through a chiral auxiliary approach, future research in this laboratory will focus on the developent of a catalytic-enantioselective variant of the method developed.

Acknowledgment. For financial support we thank the DFG (FOR 806) and the Fonds der chemischen Industrie (doctoral fellowship to P.H.).

Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) In all cases, the diastereomeric purity of the products (*trans*-*rac*-**2**) was determined by means of ^{1}H NMR (400 MHz). The nonconverted starting material (*rac*-**10**) was re-isolated as a mixture of *trans* and *cis* diastereomers.

(24) Dobarro, A.; Velasco, D. *Tetrahedron* **1996**, *52*, 13733–13738.

(25) For reviews, see: (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 20–43. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 1–24. (d) Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Nevolam, L.; Botta, B.; Zappia, G.; Cancelliere, G. *Curr. Org. Synth.* **2007**, *4*, 238–307.

(26) The ratio of the inseparable diastereomers was determined by ^{1}H NMR. The assumed *trans*-configuration of both major isomers was confirmed after hydrolysis to **2a**. The formation of minor amounts of *cis*-isomers cannot be excluded because of the complexity of the NMR spectra on the stage of **15**.

(27) The BF_3-mediated 1,4-addition of a vinyl-Cu reagent to **14** (according to Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947–959) proceeded in 82% yield, however, with lower selectivity (*dr* = 3.2:1).

(28) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

(29) The auxiliary **13** was reisolated in 57% yield. The *dr* of **15** was determined by ^{1}H NMR (integration of the H-2 signals at ca. 5.5 ppm).

(30) (a) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315–316. (b) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495–496.

(31) Dragovich, P. S.; Webber, S. E.; Babine, R. E.; Fuhrman, S. A.; Patick, A. K. *J. Med. Chem.* **1998**, *41*, 2813–2818.