Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3597–3601
Tetrahedron Letters

Synthesis, resolution and applications of 3,3′-bis(RO)-MeO-BIPHEP derivatives ☆

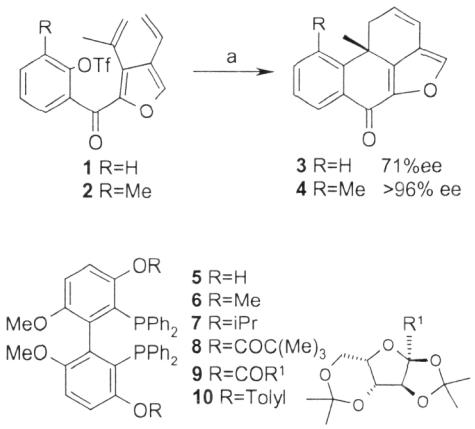
Evgueni Gorobets, Guang-Ri Sun, Bronwen M. M. Wheatley, Masood Parvez and Brian A. Keay*

Department of Chemistry, University of Calgary, Calgary, Alta, Canada T2N 1N4

Received 3 February 2004; revised 3 March 2004; accepted 10 March 2004

Abstract—A series of optically pure 3,3′-bis(RO)-MeO-BIPHEP derivatives are prepared and used in palladium catalyzed asymmetric transformations. The phosphine oxide of (±)-**5** is prepared in four steps from *p*-methoxyphenol and resolved using the novel resolving reagent chloro(L-menthoxy)dimethylsilane. Subsequent conversions provide catalysts **8** and **9**. Ligands **6**, **7** and **10** are prepared in six steps from *p*-methoxyphenol and the phosphine oxides of **6** and **7**, and **10** are resolved using di-*p*-toluoyl- and dibenzoyl-L-tartaric acid, respectively. (*R*)-3,3′-Bispivalate **8** is superior to the other catalysts in asymmetric Heck reaction with 2,3-dihydrofuran while (*R*)-(+)-bis(tolyloxy) **10** and (+)-(*R*)-sugar derivative **9** are better in the Pd-catalyzed polyene cyclization; however, the absolute sense of chirality in the product from the polyene cyclization was reversed to that obtained when (*R*)-(+)-BINAP and (*R*)-(+)-MeO-BIPHEP were used.
© 2004 Elsevier Ltd. All rights reserved.

Since we reported the synthesis of (+)-xestoquinone in 1996 in 68% ee using an asymmetric palladium catalyzed polyene cyclization (PCPC) as the key step,[1] we have been interested in finding methods for increasing the enantioselectively in palladium catalyzed polyene cyclizations **1** → **3**.[2,3] While investigating the effect of substituents on the PCPC we found that the placement of a methyl group *ortho* to the triflate, that is, **2** (Scheme 1) resulted in the formation of **4** in >96% ee when compared to 71% ee with the reaction of **1** → **3**. PM3(tm) semi-empirical calculations[4] indicated that group *ortho* to the triflate in **2** might be interacting strongly with one of the 3′ hydrogen atoms in (*S*)-BINAP after oxidative insertion of the Pd atom leading to (*S*)-**4**, while the same interaction is not observed in the isomer leading to (*R*)-**4**. Hence the %ee in the PCPC of **2** → **4** was higher than that of **1** → **3**. From these calculation and experimental results, we rationalized that if the above hypothesis is true that placement of a group other than hydrogen in the 3- and 3′-positions of BINAP should also result in an increase in the %ee in the PCPC of **1** → **3**. As the placement of substituents in the 3- and 3′-position of BINAP is not a trivial exercise,[5] we decided to focus on the development of a series 3,3′-bis(substituted)-MeO-BIPHEP[6] derivatives (**5**–**10**) in which we could systematically adjust the size of the group easily in the 3- and 3′-positions.[7,8] We herein report the synthesis, resolution and asymmetric applications of a series of new 3,3′-bis(substituted)-MeO-BIPHEP derivatives **5**–**10**.



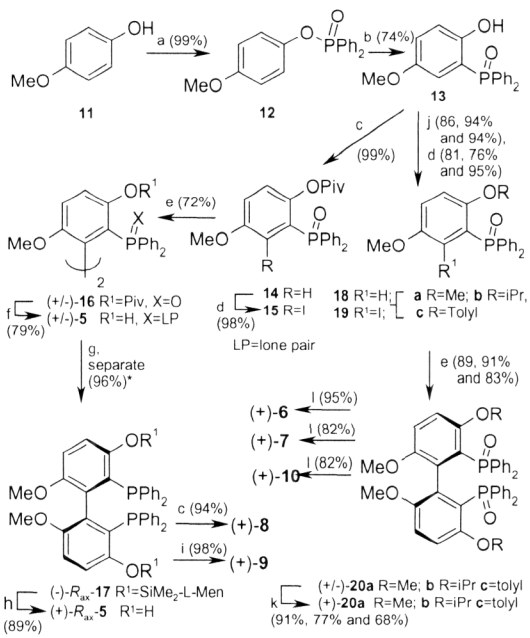
Scheme 1. Reagents and conditions: (a) $Pd_2(dba)_3$, (*S*)-BINAP, PMP, toluene, 110 °C.

Keywords: Asymmetric Heck; Asymmetric polyene cyclizations; Palladium; 3,3′-Disubstituted BIPHEP derivatives.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.03.073

* Corresponding author. Tel.: +1-403-220-5340; fax: 1-403-284-1372; e-mail: keay@ucalgary.ca

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.073



Scheme 2. Reagents and conditions: (a) Ph_2PCl, Et_3N, DCM, rt, 12 h, H_2O_2; (b) LDA, THF, −60 °C, 6 h; (c) pivalyl chloride, Et_3N, DCM; (d) LDA, THF, −75 °C, 2 h, then I_2, rt, 1 h; (e) Cu powder, DMF, 100 °C, 1.5 h; (f) AlH_3, THF, 67 °C, 12 h (79%); (g) L-menthol–Me_2SiCl, Et_3N, DCM, 0 °C, 1 d; (h) HF–pyr, THF, −70 °C to rt, 1 h; (i) 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonyl chloride, Et_3N, DMAP, DCM, rt, 30 min; (j) MeI, DMF, K_2CO_3, rt, 24 h or *i*-PrBr, DMF, K_2CO_3, 45 °C, 6 h or 4-iodotoluene, Cs_2CO_3, pyr, CuBr, 115 °C, 1 d (94%); (k) D-(+)-DTTA, 95% EtOH, separate or D-(+)-DTTA, CH_3CN, separate or L-(−)-DBTA, $CHCl_3$, separate; (l) $HSiCl_3$, xylene, 48 h, 145 °C; *48% of each diastereomer.

4-Methoxyphenol (**11**) was treated with $ClPPh_2$[9] followed by H_2O_2[10] to give **12** that was subsequently migrated to the *ortho*-position by treatment with LDA giving **13** (Scheme 2).[11] Protection of the hydroxyl group as a pivalate **14** and introduction of an iodine atom between the methoxyl and diphenylphosphonyl groups provided **15**.[6] Ullmann coupling[6,12] of **15** gave (±)-**16**, which was reduced with AlH_3[13] to give (±)-**5**. Resolution of (±)-**5** or the corresponding phosphine oxide using reported methods for BINAP[14] or MeO-BIPHEP[6] did not work and led us to develop a new resolution method for biaryl systems containing hydroxyl groups. Treatment of (±)-**5** with chloro(L-menthyloxy)dimethylsilane[15] gave two diastereomers (−)-R_{ax}-**17** (R_f 0.23) and (−)-S_{ax}-**17** (R_f 0.20) that were separated by silica gel column chromatography (hexanes/Et_2O, 20:1). The latter diastereomer crystallized from hexanes and the absolute stereochemistry was found to be S_{ax} from the X-ray crystal structure (Fig. 1).[†] Removal of the silyl group from (−)-R_{ax}-**17** and (−)-S_{ax}-**17** provided (+)-R_{ax}-**5** and (−)-S_{ax}-**5**, respectively. (+)-R_{ax}-**5** was subsequently converted into (+)-**8** and **9** using standard procedures.

[†] Compound (−)-S_{ax}-**17**: monoclinic $C2$; $a = 28.3813(7)$ Å, $b = 9.6063(2)$ Å, $c = 11.1778(4)$ Å, $\beta = 105.3695(10)°$, $V = 2938.52(14)$ Å^3; $Z = 2$; $R = 0.042$; $Rw = 0.083$.

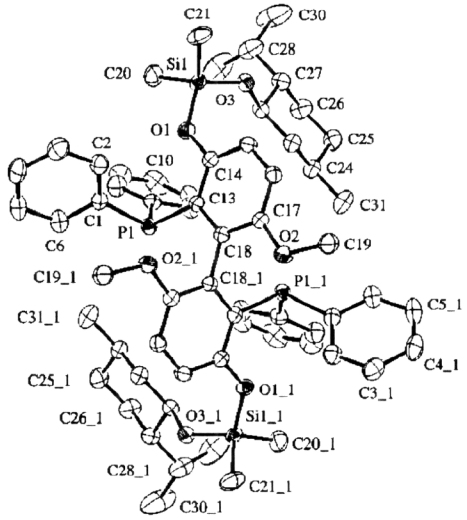


Figure 1. ORTEP diagram of (−)-S_{ax}-**17** drawn with 30% probability ellipsoids. Hydrogen atoms are represented as spheres of arbitrary size.

Compounds (+)-**6**, (+)-**7** and (+)-**10** were prepared by either alkylation of **13** with MeI or *i*-PrBr or by treatment with 4-iodotoluene in the presence of CuBr and caesium carbonate in refluxing pyridine to give **18a–c**, respectively (Scheme 2).[16] Introduction of an iodine atom (LDA, I_2) gave **19a–c**, which was subsequently Ullmann coupled to give (±)-**20a–c**. Co-crystallization of (±)-**20a** and **20b** first with di-*p*-toluoyl-D-tartaric acid (D-(+)-DTTA), filtering and a subsequent co-crystallization of the remaining mother liquor with L-(−)-DTTA in $CHCl_3$ provided (−)-**20a** and (+)-**20b**, respectively. A similar resolution on (±)-**20c** using dibenzoyl-L-tartaric acid (L-(−)-DBTA) gave (+)-**20c**. Subsequent reduction with trichlorosilane[17] gave (+)-**6**, (+)-**7** and (+)-**10**.[‡]

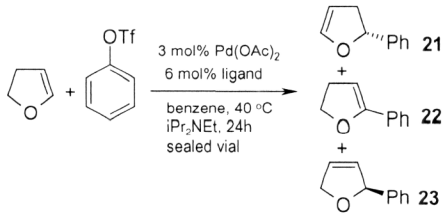
The enantiomeric purity of compounds **6**, **7** and **10** was determined by integrating the MeO signals in the ^{1}H NMR spectrum of the corresponding L-(−)-DBTA complex with the corresponding bisphosphine oxides. The enantiopurity of **5** was determined in a similar manner by examination of the ^{1}H NMR of (+)- and (−)-**17**.

With (+)-**5**–**10** in hand we compared the efficacy of these ligands in the asymmetric Heck arylation of 2,3-dihydro furan and compared the results to those obtained with (+)-BINAP[18] and (+)-MeO-BIPHEP[6] (Table 1). In our hands Hayashi's reaction conditions[19] reported with (+)-BINAP and Hunig's base at 40 °C for 24 h afforded lower product conversion and provided **21** and **23** in similar ratio and %ee[§] to that reported by Hayashi. (+)-MeO-

[‡] All compounds gave spectral data and/or elemental analyses in accordance with their structures.

[§] Enantiomeric excesses of **21** and **23** were determined from a Cyclodex-B column (30 m × 0.32 mm i.d.), which provided base line separation for each enantiomer. The retention times for (±)-**21**, **22** and (±)-**23** were 26.5/26.9, 29.1 and 31.5/31.9 min, respectively.

Table 1. Asymmetric Heck reactions with ligands **5–10**

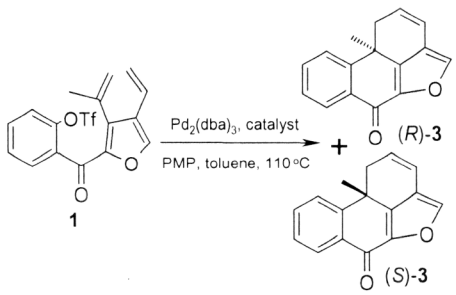


	Ligand	Conversion (%)	Ratio of products		
			21 (%ee)	**22**	**23** (%ee)
1	(+)-(*R*)-BINAP	41	91 (80)	0	9 (61)
2	(+)-(*R*)-MeO-BIPHEP	65	83 (92)	7	10 (63)
3	(+)-(*R*)-**5**	No rxn	—	—	—
4	(+)-(*R*)-**6**	6	100 (9)	0	0
5	(+)-(*R*)-**7**	37	93 (77)	0	7 (0)
6	(+)-(*R*)-**8**	**100**	**99 (90)**	**0**	**1 (10)**
7	(+)-(*R*)-**9**	48	94 (81)	0	6 (53)
8	(+)-(*R*)-**10**	57	97 (20)	0	3 (85)

BIPHEP provided a slightly higher % conversion and %ee of **21** when compared to BINAP (entry 2). Trace amounts of conjugated isomer **22** were also observed with (+)-MeO-BIPHEP.[20,21] No reaction was observed with bisphenol ligand (+)-**5** (entry 3) due to its low solubility in benzene at 40 °C and bismethoxy ligand (+)-**6** proved equally disappointing although solubility in benzene was not an issue with this ligand (entry 4). Ligands (+)-**7** (bis-*i*-PrO), **9** (bis-(sugarC=O)O) and **10** (bis-tolylO) provided similar % conversions as BINAP and MeO-BIPHEP (entries 5, 7 and 8) however the %ee of **21** was slightly lower with ligands **7** and **9** while ligand **10** gave a disappointing 20% ee of **21**. The increase in the ratio of **21**/**23** with ligands **7**, **9** and **10** is noteworthy and longer reaction times might have provided better % conversion to products. To our gratification, ligand **8** out performed both BINAP and MeO-BIPHEP by providing *100% conversion* to products after only 24 h and a much-improved ratio of **21**/**23**. The %ee of **21** was similar to those obtained with BINAP and BIPHEP. Interestingly, ligands **6–10** suppressed the formation of conjugated isomer **22**.[20]

Ligands (+)-(*R*)-**5–10** where then tried in the palladium catalyzed polyene cyclization (**1** → **3**) and compared to the results obtained with (+)-(*R*)-BINAP and (+)-(*R*)-MeO-BIPHEP (Table 2). (+)-(*R*)-BINAP and (+)-(*R*)-MeO-BIPHEP afforded (*S*)-**3** in 68% and 72% ee, respectively, although the % yield with (+)-(*R*)-MeO-BIPHEP was lower than that obtained with (+)-(*R*)-BINAP (entries 1 and 2). As above in the Hayashi reaction, ligand (+)-(*R*)-**5** did not promote the reaction

Table 2. Asymmetric Pd-catalyzed polyene cyclization results with ligands **5–10**



	Catalyst	Yield (%)	Ratio of enantiomers		Ee (%)
			(*R*)-**3**	(*S*)-**3**	
1	(+)-(*R*)-BINAP	81	**84**	16	68
2	(+)-(*R*)-MeO-BIPHEP	53	**86**	14	72
3	(+)-(*R*)-**5**	No rxn	—	—	—
4	(+)-(*R*)-**6**	69	26	**74**	48
5	(+)-(*R*)-**7**	76	30	**70**	40
6	(+)-(*R*)-**8**	67	**54**	46	8
7	(+)-(*R*)-**9**	59	18	**82**	64
8	(+)-(*R*)-**10**	71	14	**86**	72

due to solubility problems in toluene at 110 °C (entry 3). The use of pivalate ligand (+)-(*R*)-**8** was disappointing as it afforded essentially a racemic mixture of **3**. This reaction was repeated and when a similar %ee was obtained the enantiopurity of ligand (+)-(*R*)-**8** was checked but was found to a %ee of >97%. Ligands (+)-(*R*)-**6** and (+)-(*R*)-**7** provided **3** in a disappointing ee of 48% and 40%, respectively. Upon closer examination of the HPLC trace;[*] however, *it was noticed that the major isomer of the reaction in both cases was the R-isomer of* **3** and not the expected S-isomer when using a biaryl ligands with absolute stereochemistry R_{ax} (cf. entries 1 and 2, Table 2). This unexpected reversal of absolute stereochemistry in **3** was also observed with ligands (+)-(*R*)-**9** and **10** but in these cases the %ee increased to 64% and 72%, respectively (entries 7 and 8). So contrary to the expected result from PM3 semi-empirical calculations, the use of a variety of (+)-(*R*)-3,3′-bis(substituted)-MeO-BIPHEP ligands **6**, **7**, **9** and **10** did not increase the %ee of the polyene cyclization but instead provided similar %ee's of **3** as those obtained with (+)-(*R*)-BINAP and MeO-BIPHEP *but with the opposite sense of chirality*.[**]

We have shown that a variety of 3,3′-bis(substituted)-MeO-BIPHEP derivatives can be easily prepared and resolved. (+)-(*R*)-**8** proved better than BINAP and MeO-BIPHEP in the Heck reaction between phenyltriflate and 2,3-dihydrofuran while (+)-(*R*)-**6**, **7**, **9** and **10** unexpectedly provided (*S*)-**3** in the intramolecular polyene cyclization. Work is continuing to rationalize the observed reversal of absolute stereochemistry and to use ligands **5**–**10** in other transition metal catalyzed processes.

Supplementary material

Methods for double checking the assignment of absolute stereochemistry to ligands **5**–**10** is provided along with general procedures for the Heck and intramolecular polyene cyclizations.

Acknowledgements

We thank Merck Frosst (Pointe Claire, PQ), NSERC CRD program, and the University of Calgary for financial support. We thank Kristine M. Muller for a few polyene cyclization results with catalysts **5**–**7** and Thomas Wood for help with some of the syntheses. In addition NSERC and the Alberta Ingenuity Fund are thanked for postgraduate scholarships (for B.M.M.W.).

[*] The enantiomeric excesses were unequivocally determined by HPLC analysis using a Chiralcel OD-H column using *n*-hexane/isopropanol (90:10).

[**] The reversal of absolute stereochemistry in product **3** resulted in us double-checking the absolute stereochemistry assigned to ligands **5**–**10**. See the supplemental information for more details.

References and notes

1. (a) Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766–10773; (b) Keay, B. A.; Maddaford, S. P.; Cristofoli, W. A.; Andersen, N. G.; Passafaro, M. S.; Wilson, N. S.; Nieman, J. A. *Can. J. Chem.* **1997**, *75*, 1163–1171; (c) Cristofoli, W. A.; Keay, B. A. *Synlett* **1994**, 625–627.
2. (a) Lau, S. Y. W.; Keay, B. A. *Synlett* **1999**, 605–607; (b) Lau, S. Y. W.; Andersen, N. G.; Keay, B. A. *Org. Lett.* **2001**, *3*, 181–184; (c) Che, D.; Andersen, N. G.; Lau, S. Y. W.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1919–1925; (d) Andersen, N. G.; McDonald, R.; Keay, B. A. *Tetrahedron: Asymmetry* **2001**, *12*, 263–269.
3. For recent reviews involving Pd-cat polyene reactions, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963; (b) deMeijere, A.; Brase, S. *J. Organomet. Chem.* **1999**, *576*, 88–110; (c) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65–87; (d) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111–124; (e) Takahasi, T.; Doi, T.; Yamamoto, K. In *Transiton Metals for Organic Synthesis*; Beller, M, Bolm, C, Eds.; Wiley-VCH: Weinheim, 1998; Vol. 1, pp 265–274.
4. Spartan 4.1.1, Deppmeier, B. J.; Driessen, A. J.; Hehre, W. J.; Johnson, J. A.; Johnson, H. C.; Leonard, J. M.; Lou, L.; Peng, C.; Yu, J.; Baker, J.; Carpenter, J. E.; Dixon, R. W.; Fielder, S. S.; Kahn, S. D.; Pietro, W. J. Wavefunction, Inc., Irvine, CA, 1996.
5. Lau, S. Y. W. PhD Dissertation, University of Calgary, Calgary, AB, Canada, 2002.
6. (a) Schmid, R.; Cereghetti, M.; Heiser, B.; Schonholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897; (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370–389.
7. In 1991 the first report of a 3,3′-disubstitued-MeO-BIPHEP appeared in which Brown and Woodward prepared compound **6** as the phosphine oxide. No further transformations with this compound could be found in the literature. Brown, J. M.; Woodward, S. *J. Org. Chem.* **1991**, *56*, 6803–6809.
8. While our work was in progress, Zhang and co-workers reported the synthesis, resolution and application of a 3,3′-bis(substituted)-MeO-BIPHEP derivative called *o*-Ph-HexaMeO-BIPHEP. (a) Tang, W.; Chi, Y.; Zhang, X. *Org. Lett.* **2002**, *4*, 1695; (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069.
9. Hall, T. J.; Hargis, J. H. *J. Org. Chem.* **1986**, *51*, 4185–4189.
10. Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691–694.
11. Petros, K. A.; Agafonov, S. V.; Pokatun, V. P. *J. Gen. Chem. USSR* **1987**, *57*, 83–85.
12. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
13. (a) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464–1472; (b) Griffin, S.; Heath, L.; Wyatt, P. *Tetrahedron Lett.* **1998**, *39*, 4405–4406.
14. Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245–1253.
15. (a) Wei, Z. Y.; Wang, D.; Li, J. S. *J. Org. Chem.* **1989**, *54*, 5768–5774; (b) Kaye, P. T.; Learmonth, R. A. *Synth. Commun.* **1989**, *19*, 2337–2344.
16. Various methods for the preparation of diaryl ethers gave unreacted starting materials thus we developed our own procedure. For previous diaryl ether syntheses, see: (a) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540; (b) Tomita, M. *Chem. Pharm. Bull.* **1965**, *13*, 1341–1345; (c) Gujadhur, R. K.;

Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4318.
17. Takaya, H.; Mashima, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629–635.
18. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
19. (a) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188; (b) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.
20. To our knowledge we were the first to report the formation of conjugated isomer **22** in the Heck reaction between phenyltriflate and 2,3-dihydrofuran.[21] This led us to investigate the mechanism of this reaction in more detail. For more information, see: Andersen, N. G. PhD Dissertation, University of Calgary, Calgary, AB, Canada, 2001.
21. Andersen, N. G.; Parvez, M.; Keay, B. A. *Org. Lett.* **2000**, *2*, 2817.