Tetrahedron Letters, Vol. 34, No. 50, pp. 8063-8066, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

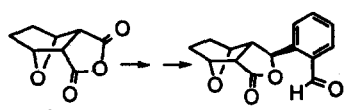
# A Novel and Highly Efficient Desymmetrization of a *Meso*-Anhydride by a Chiral Grignard Reagent

Sharon D. Real,* David R. Kronenthal and Helen Y. Wu

The Bristol-Myers Squibb Pharmaceutical Research Institute
P.O. Box 4000, Princeton, New Jersey 08543-4000, USA

***Abstract:*** *The addition of the chiral oxazolidine Grignard 3c to anhydride 1, followed by in situ $NaBH_4$ reduction and acid hydrolysis, provides aldehyde 2 in greater than 98% enantiomeric excess.*

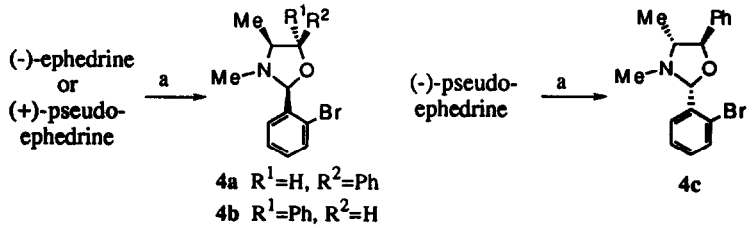
In connection with our thromboxane antagonist program, we needed to develop an efficient process to convert prochiral anhydride **1** to chiral **2**, a key intermediate[1] in the synthesis of the clinical candidate **BMS 180,291**.[2] One efficient method to prepare **2** would involve desymmetrization of **1** with an aryl metal substituted in the *ortho* position with a chiral auxiliary at the aldehyde oxidation level. In this communication we describe the realization of this goal by the highly diastereoselective addition of aromatic, chiral oxazolidines (e.g. **3c**) to **1** to give, after *in situ* sodium borohydride reduction and acid hydrolysis, **2** in greater than 98% enantiomeric excess.



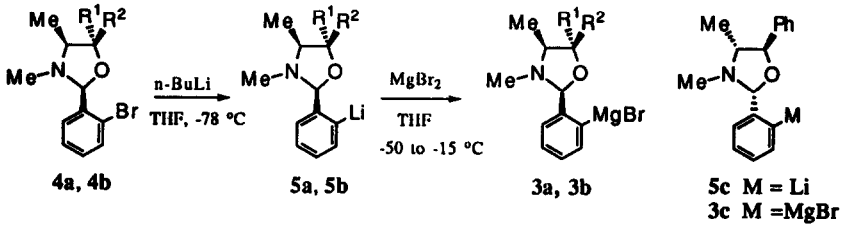
**1** **2**

While desymmetrizations of *meso*-anhydrides by chiral heteroatom nucleophiles[3] and hydrides[4] are known, we are unaware of any precedent for the same process using carbanions. *Ortho*-metalated chiral aminals,[5] acetals,[5,6] and oxazolidines[7] have been added to aldehydes with moderate to high diastereoselectivities; however, the high cost or multi-step preparation of the precursor diamines, diols, and amino alcohols precludes their use in our synthesis. Instead, we wished to apply similar methodology to the desymmetrization of **1** utilizing inexpensive and commercially available chiral amino alcohols such as ephedrine or pseudoephedrine.

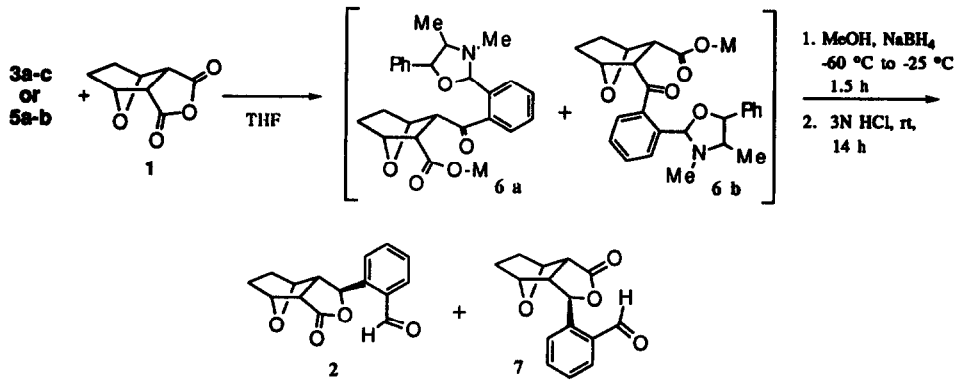
As previously reported,[8] aryl oxazolidines can be synthesized from chiral amino alcohols with high diastereoselectivity. Condensation of *ortho*-bromobenzaldehyde with (-)-ephedrine, (+)-pseudoephedrine, and (-)-pseudoephedrine produced **4a-c** respectively (Scheme 1).[9] Oxazolidine **4a** was a solid which was crystallized from ethanol to give a single diastereomer (83% yield). Oxazolidines **4b** and **4c** were obtained in quantitative yield as a mixture of two diastereomers (40:1 and 38:1 respectively,[10] minor diastereomer not shown). These mixtures were oils that were inseparable by silica gel chromatography. Consequently, they




**Scheme 1.** a) *ortho*-bromobenzaldehyde, toluene, reflux, Dean-Stark




**Scheme 2.** a series: $R^1$=H, $R^2$=Ph; b series: $R^1$=Ph, $R^2$=H




**Scheme 3**

were carried on to subsequent steps as crude material.

Treatment of **4a-4c** with n-BuLi (1 equiv, THF, -78 to - 60 °C) produced a solution of aryl lithium derivatives **5a-5c** (Scheme 2) which could be further transformed into Grignard reagents **3a-3c** by cannulation into a THF solution of $MgBr_2$[11] (1.2 equiv, -50 to -15 °C, 0.5 h). Addition of **1** (1 equiv) to the (-)-ephedrine-derived Grignard **3a** (1.4 equiv, THF, -60 to -30 °C, 3h) produced a solution of ketones **6a** and **6b** (Scheme 3) which were further converted to 2 and 7 by quenching with methanol (-60 °C), addition of $NaBH_4$ (1.4 equiv, -60 to -25 °C, 1.5 h)[12,13] and acid hydrolysis (3N HCl, 6 equiv, 25 °C, 14 h). Extractive workup followed by silica gel chromatography produced the undesired enantiomer **7** in 66% ee

**Table 1** Reaction of **1** with Chiral Organolithium or Grignard Reagents

| Reagent | Counter-ion | Product[a] | Yield (%) | ee (%)[b] | Reagent | Counter-ion | Product[a] | Yield (%) | ee (%)[b] |
|---|---|---|---|---|---|---|---|---|---|
| **5a** | Li | **2** | 41 | 26 | **3b** | MgBr | **7** | 65 | 99.0 |
| **5b** | Li | **2** | 51 | 30 | **3c** | MgBr | **2** | 64[c] | 99.2[d] |
| **3a** | MgBr | **7** | 56 | 66 | | | | | |

[a]The absolute configuration was determined by comparison with the known compound (both by specific rotation and chiral chromatography).
[b]The enantiomeric excess was determined by chiral HPLC using a Chiralpak AD column on material purified by silica gel chromatography.
[c]Crystallized yield from THF/0.5N HCl
[d]Enantiomeric excess of crystallized product. Chiral HPLC analysis of crude product showed **2** to be formed in 98.3% ee

(56% yield from **1**).[14] The asymmetric induction was further increased by using the pseudoephedrine-derived Grignard reagents **3b** and **3c**. Reaction of **3b** with **1** followed by *in situ* $NaBH_4$ reduction and acid hydrolysis gave **7** in 99.0% ee (65% yield from **1**). The same reaction conditions with the enantiomer of **3b** (**3c**) gave the predicted desired product **2**[15,16] in 99.2% ee (64% yield starting from 6.0 g of **1**). Interestingly, the lithium derivatives **5a** and **5b** gave inferior and opposite diastereoselectivities on addition to **1** (**2** was formed in 25% and 30% ee, respectively) compared with the corresponding Grignard reagents (**3a** and **3b** respectively).[17] These results are summarized in Table 1.

The reasons for the excellent selectivity of the Grignard reagents, the poor and opposite selectivity of the lithium reagents (**5a** and **5b**), and the enhanced diastereoselectivity observed with the pseudoephedrine-derived oxazolidine **3c** relative to the ephedrine-based derivative **3a** are under investigation. Further studies on the desymmetrization of *meso*-anhydrides with carbanions will be reported in due course.

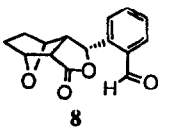
## Acknowledgments

We are grateful to Ms. Barbara De Lange, Mr. James McCarthy, and Ms. Sue Taylor for the chiral HPLC data; Ms. Yolanda Pan for the NOE experiments and Dr. Jack Gougoutas for the crystal structure analysis. We are also grateful to Drs. Mark Schwinden, Andrew Pudzianowski, Edward Vawter and Xuebao Wang for valuable discussions. We would also like to acknowledge Dr. Truc Vu for preliminary work in the area of asymmetric additions of Grignard reagents to *meso*-anhydrides.

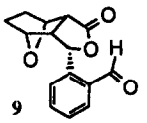
## References and Notes

1. Thottathil, J.; Pansegrau, P.; Poss, M.; Wang, S. U.S. Patent pending.
2. Misra, R.N.; Brown, B.B.; Sher, P.M.; Patel, M.M.; Hall, S.E.; Han, W-C; Barrish, J.; Floyd, D.M.; Sprague, P.W.; Morrison, R.A.; Ridgewell, R.E.; White, R. E.; DiDonato, G.C.; Harris, D. N.; Hedberg, A.; Schumacher, W. A.; Webb, M. L.; Ogletree, M. L. *BioMed. Chem. Lett.* **1992**, *2*, 73.
3. a) Suda, Y.; Yago, S.; Shiro, M.; Taguchi, T. *Chem. Lett.* **1992**, 389 and references therein. b) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1 and references therein. b) Thottathil, J. U.S. Patent **1987**, US 4743697.
4. Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett.* **1993**, *34*, 1167 and references therein.

5. Commercon, M.; Mangeney, P.; Tejero, T.; Alexakis, A. *Tetrahedron: Asymmetry* **1990**, *1*, 287.
6. Kaino, M.; Ishihara, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3736.
7. Takahashi, H.; Tsubuki, T.; Higashiyama, K. *Synthesis* **1992**, 681.
8. a) Soliman, S. A.; Abdine, H.; El-Nenaey, S. *Aust. J. Chem.* **1975**, *28*, 49. b) Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537 and references therein.
9. The relative configurations of **4a** and **4b** were confirmed by NOE experiments. The relative configuration of **4a** was also confirmed by an X-ray crystal structure.
10. The ratio of the major to minor diastereomers was determined by $^1$H NMR analysis.
11. The magnesium bromide was freshly prepared *in situ* from magnesium and 1,2-dibromopropane or 1,2-dibromoethane in THF.
12. The sodium borohydride reduction of the intermediate ketones is highly diastereoselective only if magnesium ion is present, giving rise to predominately one lactone epimer (**2+7** verses **8+9**, see also footnote 17). Typical epimer ratios are 99.7:0.3 (**2+7** : **8+9**) as determined by chiral HPLC. For the benzylic proton in **2** and **7**, J=2.9 Hz; for **8** and **9**, J=6.5 Hz. The epimer configuration for **2** was confirmed by NOE experiments.



**8**



**9**

13. TLC analysis during the sodium borohydride reduction showed the reaction to be complete, thus indicating that no kinetic resolution occurred at this stage.
14. The enantiomeric purity was determined by chiral HPLC on the product purified by silica gel chromatography.
15. For **2**: (mp 133.5-135.0 °C); $[\alpha]_D$ -187.0° (c 1.0, 95% EtOH); $^1$H NMR (270 MHz, $CDCl_3$) δ 10.09 (s, 1H), 7.91 (dd, J=1.8, 7.0 Hz, 1H), 7.45-7.75 (m, 3H), 6.08 (d, J=2.9 Hz, 1H), 5.34 (d, J=4.7 Hz, 1H), 4.91 (d, J=4.7 Hz, 1H), 2.88 (d, J=8.2 Hz, 1H), 2.29 (dd, 2.9, 8.2 Hz, 1H), 1.65-1.85 (m, 2H). 1.25-1.60 (m, 2H); $^{13}$C NMR (67.8 MHz, $CDCl_3$) δ 193.3, 177.6, 142.4, 136.4, 134.3, 131.8, 128.4, 125.0, 83.0, 82.1, 79.9, 52.5, 49.9, 28.1, 28.0.
16. In a single attempt, the chiral auxiliary, (-)-pseudoephedrine, was recovered in approximately 75% yield (unoptimized).
17. When the nucleophiles were the aryl lithium reagents **5a** and **5b**, magnesium bromide etherate was added to the reaction mixture after addition of the methanol, but prior to the addition of sodium borohydride, to minimize formation of the epimers **8** and **9**. Typical epimer ratios with magnesium ion present were greater than 99.7:0.3 (**2+7** : **8** +**9**). Typical ratios without magnesium ion present were 60:40 (**2+7** : **8** +**9**).

(Received in USA 22 June 1993; accepted 11 October 1993)