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Asymmetric Friedel-Crafts Reaction Mediated by New Chiral Auxiliaries Derived From (1S)-(-)-β-Pinene: Enantioselective Synthesis of (-)-8-Norethyl, 1'-Normethyl Etodolac

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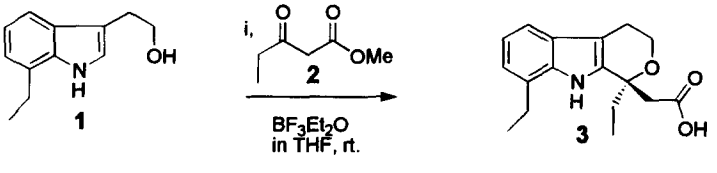
Abstract: (-)-8-Norethyl, 1'-normethyl Etodolac (-)-7 was synthesized in ee up to 95% from a Friedel-Crafts alkylation reaction between tryptophol **4** and the chiral β-ketobutyrate **5h**, followed by hydrolysis. © 1997 Elsevier Science Ltd.

Friedel-Crafts and related reactions allow the formation of C-C bonds from carbenium ions or equivalent species and aromatic or unsaturated aliphatic compounds.[1] Although they have been extensively employed in organic synthesis,[2] the stereoselectivity in these reactions have been less adressed.[3] Only a few examples of asymmetric Friedel-Crafts reaction have been reported in the literature using either pro-chiral electrophiles in the presence of covalently bonded chiral auxiliaries[4,5] or pro-chiral electrophiles in the presence of chiral Lewis acids.[6] Two cases of enantiospecific Friedel-Crafts reaction have also recently been reported.[7]

Etodolac **3**, a non steroidal antiinflamatory agent used in clinical treatment, was prepared[8] by a Friedel-Crafts alkylation reaction between 7-ethyltryptophol **1** and the β-ketoester **2**, followed by hydrolysis (scheme 1). The (+)-(*S*)-**3** enantiomer, obtained by chemical resolution, proved to be 2.6 times more active than the racemate.[9]



ii,KOH, MeOH, H_2O; iii, (-)-Borneol, DCC, DMAP

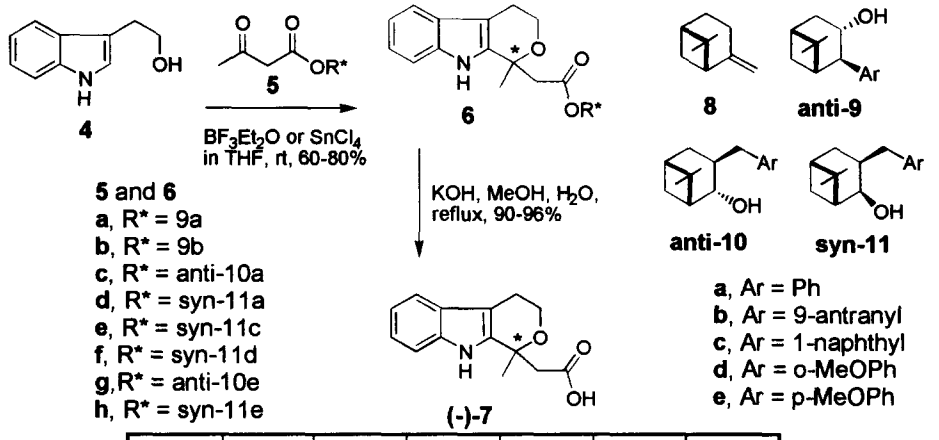
iv, Prepararive HPLC, then KOH, MeOH, H_2O

Scheme 1 : Preparation of (+)-(S)-Etodolac

Recently we described[10] an enantioselective synthesis of the Etodolac core based on the racemic synthesis previously described by Humber (Scheme 2, entries 1-3). Etodolac analog, 8-norethyl,1'-normethyl Etodolac (-)-7 was prepared in modest de by reaction of chiral β-ketobutyrates **5a** or **5b** with tryptophol **4** , followed by hydrolysis of the resulting ester **6a** or **6b**. The β-ketobutyrates **5a** and **5b** were prepared through acetoacetylation of chiral auxiliaries *anti*-**9a** and *anti*-**9c**, previously synthesised from

(*1S*)-(-)-β-pinene **8**.[11] The comparison of entries 1-3 shows that the de of ester **6** increase with the size of the aromatic appendage attached to the pinane moiety.

In this paper we describe the results obtained when the new chiral auxiliaries *anti*-**10a**, *anti*-**10e**, *syn*-**11a** and *syn*-**11c-e**, also prepared from **8**,[12] were used in the enantioselective synthesis of (-)-**7** (scheme 2, entries 4-15).



Entry	6	R*	L.A.	% 6	%de	$[\alpha]_D$ 7
1	**a**	**9a**	BF_3	87	10	
2	**b**	**9b**	BF_3	81	40	-8.54
3	**b**	**9b**	$SnCl_4$	70	36	
4	**c**	**10a**	BF_3	68	0	
5	**c**	**10a**	$SnCl_4$	61	0	
6	**d**	**11a**	BF_3	58	73	
7	**d**	**11a**	$SnCl_4$	57	84	-18.0
8	**e**	**11c**	BF_3	85	10	
9	**e**	**11c**	$SnCl_4$	73	0	
10	**f**	**11d**	BF_3	80	0	
11	**f**	**11d**	$SnCl_4$	78	24	
12	**g**	**10e**	BF_3	61	0	
13	**g**	**10e**	$SnCl_4$	59	0	
14	**h**	**11e**	BF_3	65	0	
15	**h**	**11e**	$SnCl_4$	59	>95	-20.2

Scheme 2: Enantioselective Synthesis of (-)-7 Mediated by Chiral Auxiliaries Derived From (-)-β-Pinene

As shown in entries 4 and 5, the use of chiral β-ketobutyrate **5c** led to ester **6c** as a equimolecular mixture of epimers at the newly created quaternary asymmetric center, regardless of the Lewis acid employed as catalyst. On the other hand, the reactions involving *syn*-**11a** (β-ketoester **5d**) led to **6d** in good de (entries 6 and 7). In order to improve this diastereoselectivity, the auxiliary *syn*-**11c** (β-

ketobutyrate **5e**), bearing a more bulky aromatic appendage, was studied. In contrast to the previously observed for **9** (entries 1-3), the reactions mediated by *syn*-**11b** led to disapointing de (entries 8 and 9).

Finally we studied the chiral auxiliaries *syn*-**11d-e** and *anti*-**10e**, having a methoxy substituent on the aromatic appendage (entries 10-15). We speculated that chelated transition states would be originated, involving the metal, the carbonyl groups in the β-ketoester moiety and the methoxy group at the aromatic ring of the chiral auxiliar moiety allowing a better π-facial discrimination of the keto group. When *syn*-**11d** and *anti*-**10e** (β-ketobutyrates **5f** and **5g**) were used in the synthesis of **6**, disappointing results were obtained regardless of the Lewis acid employed (entries 10-13). However, for *syn*-**11e** the de was very dependent on the Lewis acid employed. While a mixture of equimolecular of epimers of **6h** were formed when BF_3 Et_2O was used as catalyst, a de of up to 95% was obtained when the Lewis acid employed was $SnCl_4$.[13] Removal of the chiral auxiliary by saponification gave (-)-**7** (ee up to 95%) and recovered *syn*-**11**.[14]

In conclusion, our results allow the synthesis of the Etodolac core, in excellent enantiomeric excess using the readily prepared chiral auxiliaries *syn*-**11a** and *syn*-**11e**, derived from (1S)-(-)-β-pinene (**8**). Since (1R)-(+)-β-pinene is available from isomerization of (1R)-(+)-α-pinene,[15] the enantiomers of *syn*-**11a** and *syn*-**11e** can be easily prepared, allowing the enantioselective synthesis of (+)-**7**. Work is in progress to determine the absolute configuration of (-)-**7**. The use of this strategy to prepare (+)-(S)-Etodolac (**3**) is also under investigation.

References and Notes

1 (a) Olah, G.A. ; Khrisnamurti, R.; Surya Prakash, G.K. in *Comprehensive Organic Chemistry*, w Ed; **1991**, Vol w, 293-339.(b) Roberts, R.M.; Khalaf, A. A. in *Friedel-Crafts Alkylation Chemistry. A Century of Discovery*, Dekker, New York, 1984.(c) For a Friedel-Crafts reaction based on palladium catalysis see inter alia: Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajaah, V. *Tetrahedron Lett.* **1995**, *36*, 8137-8140.

2 (a) Danheiser, R.L.; Casebier, D.S.; Firooznia,F. *J. Org. Chem.* **1995**, *60*, 8341-8350. (b) De Lombaert,S.; Blanchard, L.; Stanford, L. B.; Sperbeck, D.M.; Grim, M. D.; Jenson, T. D.; Rodrigues, H. R. *Tetrahedron Lett.* **1994**, *35*, 7513-7516. (c) Xiao, D.; Schreier, J. A.; Cook, J. H.; Seybold, P. G.; Ketcha, D. M. *Tetrahedron Lett.* **1996**, *37*, 1523-1526. (d) Cabral, L. M.; Barreiro, E. J. *J. Heterocyclic Chem.* **1995**, *32*, 959-962.

3 For diastereoselective Friedel-Crafts reaction see: (a) Yoshimatsu, M.; Takashi, S.; Shimizu, H.; Hori, M.; Kataoka, T. *J. Org. Chem.* **1994**, *59*, 1011-1019. (b) Olah, G. A.; Lee, C. S.; Prakash, G. K. S.*J. Org. Chem.* **1994**, *59*, 2590-2593. (c) Matsumoto, T.*Tetrahedron Lett.* **1988**, *29*, 3559-3562. (d) Timothy, A. G.; Twtchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468-2477.

4 (a) El Kaim, L.; Guyoton, S.; Meyer, C. *Tetrahedron Lett.* **1996**, *37*, 375-378. (b) Brown, D. S.; Earle, M..J.; El Gihani, M. T.; Heaney, H. *Synlett* **1995**, 2694-2996. (c) Bigi, F.; Sartori, G.; Maggi, R.; Cantarelli, E.; Galaverna, G. *Tetrahedron:Asymmetry* **1993**, *4*, 2411-2414.

5 Chiral versions for the Picted-Spengler reaction, a aza analogous process, have been recently reported: (a) Cox, E.D.; Hameker, L.K.; Li, J.; Yu,P.; Czerwinski, K.M.; Deng, L.; Bennett, D.W.; Cook, J.M. *J.Org.Chem.* **1997**, *62*, 44-61 See also references cited therein. (b) Dai, W.M.; Zhu, H.J.; Hao, X.-J. *Tetrahedron:Asymm*etry **1996**, *7*, 1245-1298. (c) Dai, W.-M.; Zhu, H.J.; Hao,X.-

J. *Tetrahedron Lett.* **1996**, *37*, 5971-5974. (d) Soe, T.; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *42*, 347-358. (e) Waldmann, H.; Schimdt, G.; Jansen, M.; Geb, J. *Tetrahedron* **1994**, *50*, 1965-1968.

6 Terada, M.; Sayo, N.; Mikami, K. Synlett **1995**, 411-415.

7 (a) Muehldorf, A. V.; Guzman-Perez, A.; Kluge, A. F. *Tetrahedron Lett.* **1994**, *35*, 8755-8758. (b) Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Synlett* **1996**, 465-467.

8 Demerson, C. A.; Humber, L. G.; Philipp, A. H.; Martel, R. R. *J. Med. Chem.* **1976**, *19*, 391-395.

9 Demerson, C. A.; Humber, T. A. *J. Med. Chem.* **1983**, *26*, 1778-1780.

10 Cabral, L. M.; Costa, P. R. R.; Vasconcellos, M. L. A. A.; Barreiro, E. J.; Castro, R. N. *Synth.Comm.* **1996**, *26*, 3671-3676.

11 Vasconcellos, M. L. A. A.; d'Angelo, J.; Desmaele, D.; Costa, P. R. R.; Potin, D. *Tetrahedron:Asymmetry* **1991**, *2*, 353-356.

12 Dumas, F.; Alencar, K.G.; Mahuteau, J.; Barbero, M.J.; Miet, C.; Gérad, F.; Vasconcellos, M. L. A. A.;Costa, P. R. R. *Tetrahedron:Asymmetry* **1997**, 8, 579-582.

13 Diastereomeric ratios in **6** were determinated by quantitative ^{13}C NMR. For **6h**: Major epimer ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.09, 22.80, 24.83, 25.04, 27.15, 30.89, 32.55, 35.76, 38.28, 40.50,45.10, 45.84, 54.73, 60.31, 72.09, 76.66, 106.30, 110.10, 117.90, 119.00, 121.50, 113.4, 123.30, 129.10, 132.00, 135.40, 137.00, 171.60; (172.00,*minor epimer*).

14 $[\alpha]^{22}_D$ - 20.8 (c = 3.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 3H), 2.79-2.86 (m,2H), 2.97-2.98 (ls,2H), 4.05-4.10 (t, J=4.15Hz,2H), 6.98-7.51 (m,4H), 8.83 (NH) HRMS: Calcd. for $C_{14}H_{15}NO_3$, Found 245.104978

15 Brown, H. C.; Zaidlewicz, M. *J. Org. Chem.* **1989**, *54*, 1764-1766.

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