Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 901–905

TETRAHEDRON: *ASYMMETRY*

Refined enantioselective methylation catalysts: improved routes to bifunctional C5 synthons

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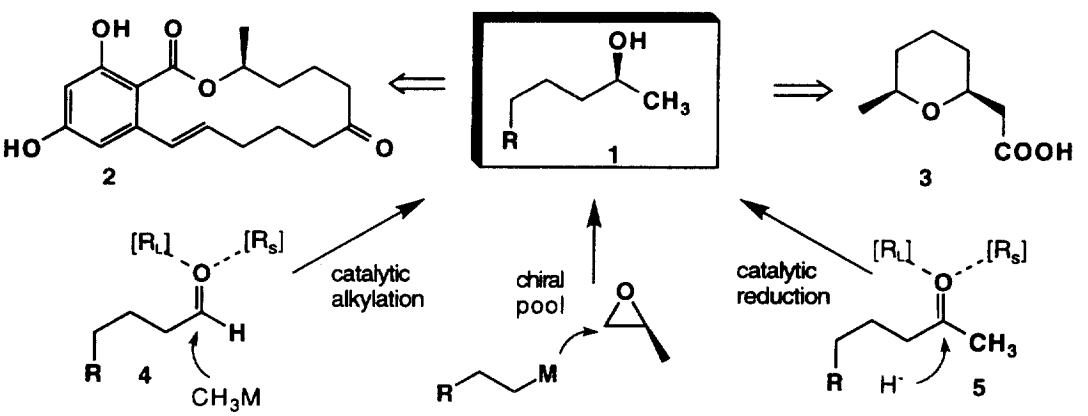
Received 19 December 1997; accepted 4 February 1998

Abstract

Catalytic enantioselective routes to bifunctional C5 synthons, including those of the macrolide (*S*)-(−)-zearalenone have been achieved. Stereochemistry was introduced using a mixed ligand arene chromium tricarbonyl catalyst to mediate the enantioselective addition of dimethyl zinc to a functionalized aldehyde. Comparison with alternate reduction strategies is presented.

Synthesis of bifunctional (*S*)-2-pentanol synthons represents an important endeavor due to the range of natural products accessible using these building blocks, including the estrogenic mycotoxin zearalenone **2** and the secretory product of *Viverra civetta* **3** (Scheme 1).[1,2] Traditional routes involving commercially available (*S*)-propylene oxide, while often expeditious, suffer from the prohibitive cost of this reagent in optically pure form.[3]



Scheme 1. Complimentary strategies for enantioselective formation of *S*-carbinols

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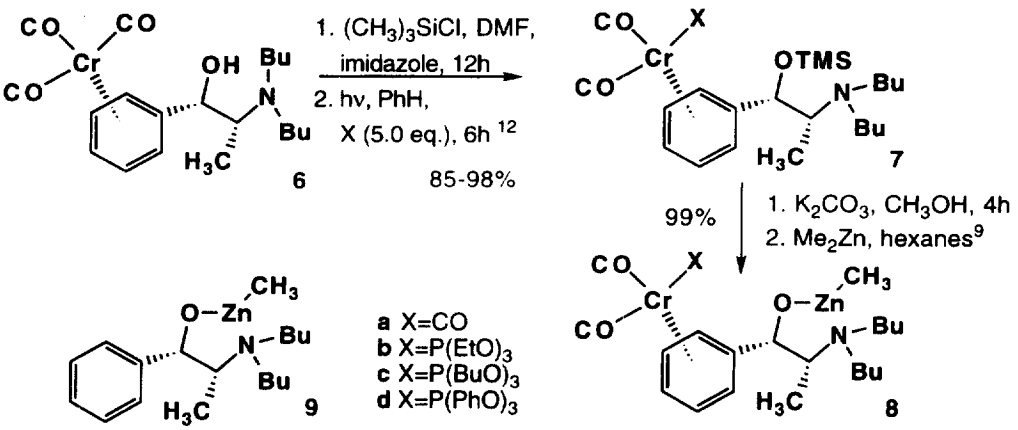
0957-4166/98/$19.00
PII: S0957-4166(98)00076-7

Based on earlier studies in the synthesis of macrolides,[4–6] we sought to demonstrate an effective catalytic route to synthons **1** (R=functional group). We reasoned that enantioselective *re* face methylation of the appropriate aldehyde **4** would prove effective, a consequence of appendage R_L presenting a local steric volume significantly different from R_S in a chiral Lewis acid complex (Scheme 1). By analogy, the alternative approach to product **1**, a Lewis acid catalyzed reduction onto the *re* face of **5** using the now popular chiral oxazaborolidine reagents, would be expected to afford inferior control, due to poor (coordinative) discrimination of R_L and R_S.[7]

Our most effective alkylation catalysts to date have been zinc alkoxides derived from chromium tricarbonyl complexed chiral amino alcohols, e.g. the (1*S*,2*R*)-dialkylnorephedrine **6**, which can mediate the addition of dialkyl zincs to aldehydes giving *S* carbinols in up to 99% e.e.[8,9] The beneficial stereodirective capacity of the arene chromium tricarbonyl group is easily demonstrated by comparison with uncomplexed analogs, e.g. **9**.[10,11] In the addition of dimethylzinc however, inferior e.e.s are often observed, particularly with alkyl aldehyde substrates or when (masked) functional groups are present in the substrate.[9] Based on our transition state model for these catalysts,[9] we reasoned that increasing the steric bulk on the metal carbonyl appendage would further increase coordinative discrimination of alkyl aldehydes to the catalyst–substrate complex, and prepared a series of mixed ligand complexes **8a–d** from **6**, via photolytic substitution,[12] best achieved via intermediate O-protection (Scheme 2).[13a]



Scheme 2. Preparation of mixed ligand arene chromium carbonyl catalysts

Zinc alkoxides **8** were prescreened in the enantioselective methylation of benzaldehyde using 10 mol% catalyst.[9] Gratifyingly, the system responded favorably to further increase in steric bulk, a trend that had failed to materialize in other classes of catalysts.[14] The most effective of these, **8d**, gave among the highest selectivity ever reported for aldehyde methylation, and is clearly superior to the lesser encumbered alkoxides **8a–c** and **9**. Selectivity did not suffer even when using 5 mol% catalyst, although 98% e.e. was still the maximum attainable using 20 mol% catalyst (Table 1).

With a more efficient catalyst for the production of *S*-carbinols secured, we turned our attention toward functionalized substrates. Accordingly, butane-1,4-diol was converted into a variety of masked hydroxyaldehydes **4** (Scheme 1).[13b] Asymmetric methylation was then conducted using the catalysts **8**, which gave the expected *S* enantiomeric alcohols **1** with good enantioselectivity (Table 2).[9] Remote ether substituents are known to play a detrimental role in the coordination process, and the highest selectivity was obtained using the trityloxy protecting group (**4**, R=OTr).[6] As previously observed the order of selectivity for the catalysts was **8d>8c>8b>8a≫9**. We were also interested in direct comparison of this approach with alternative methods, including chemical and enzymatic ketone reduction. Thus,

Table 1
Enantioselective methylation of benzaldehyde using catalysts **8**[a]

Entry	catalyst	mol%**8**	% yield[b]	%e.e.[c]
1	**9**	10	95	81
2	**8a**	10	93	90
3	**8b**	10	92	95
4	**8c**	10	99	96
5	**8d**	10	99	98
6	**8d**	20	99	98
7	**8d**	5	95	98

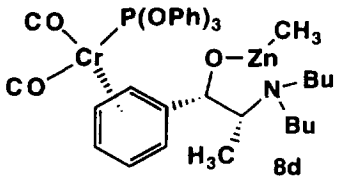
(a)All reactions employed 1.0 mmol substrate with 4 eq. $ZnMe_2$ in toluene-hexanes (16h / 0°C)[a]; (b) isolated yield of *S*-2-phenethyl alcohol; (c) determined by HPLC (Diacel OD column).

Table 2
Complimentary enantioselective routes to **1**

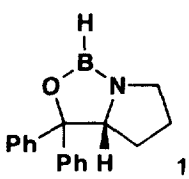
Entry	substrate	R	conditions	time	yield**1**	e.e.**1**
1	**4**	OTPS	0.1 **8a**, Me_2Zn	12h / 0°C	88%	86%[a]
2	**4**	Cl	0.1 **8a**, Me_2Zn	12h / 0°C	91%	75%[b]
3	**4**	OBn	0.1 **8a**, Me_2Zn	12h / 0°C	92%	87%[a]
4	**4**	OTr	0.1 **8a**, Me_2Zn	18h / 0°C	94%	89%[a]
5	**4**	OTr	0.1 **8b**, Me_2Zn	18h / 0°C	90%	94%[a]
6	**4**	OTr	0.1 **8c**, Me_2Zn	18h / 0°C	91%	95%[a]
7	**4**	OTr	0.1 **8d**, Me_2Zn	18h / 0°C	82%	96%[a]
8	**4**	OTr	0.2 **8d**, Me_2Zn	18h / 0°C	87%	**98%**[a]
9	**4**	OTr	0.1 **9**, Me_2Zn	18h / 0°C	91%	59%[a]
10	**5**	OTr	0.2 **10**, BH_3	2h / 25°C	92%	85%[a]
11	**5**	OTr	0.2 **11**, BH_3	2h / 25°C	89%	59%[a]
12	**5**	OTr	0.2 **12**, BH_3	2h / 25°C	99%	69%[a]
13	**5**	OTBS	TBADH / NADP	48h / 37°C	12%	83%[c]
14	**5**	OTBS	SADH / NADP	48h / 37°C	36%	94%[c]

% e.e. determined by : (a) HPLC analysis; (b) optical rotation;[18] (c) by derivitization (TPS ether) and subsequent HPLC analysis.

derivitization of 3-acetyl-1-propanol gave keto substrates **5**.[13c] A variety of oxazaborolidine catalysts were surveyed for the reduction of **5** including those derived from (*R*)-proline **10**,[15] (+)-pseudoephedrine **11**,[16] and (1*R*,2*S*)-*cis*-aminoindanol **12**.[17] In each case examined, inferior selectivity was observed, attributable to the lack of stereodifferentiation about the *re*/*si* faces of the keto group (Scheme 1). Enzymatic reduction using alcohol dehydrogenase, either from *Thermoanaerobium brockii* (TBADH)[18] or *Thermoanaerobacter ethanolicus* (SADH)[19] was also examined in the case of the more (aqueous) soluble substrate **5** (R=OTBS). Though selectivity was high, chemical yields were low even under optimized conditions.



8d



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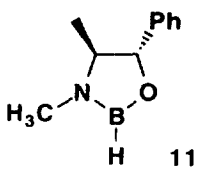

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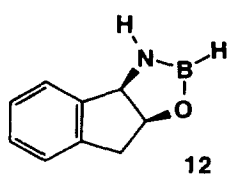

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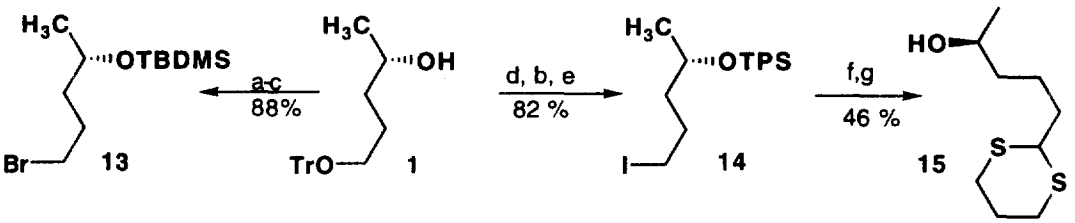
Since product **1** (R=Cl) has been used directly in the synthesis of **3**,[17] we sought to demonstrate application of **1** (R=OTr) in the preparation of key synthons for zearalenone **2**. In the syntheses of (*S*)-(−)-**2** reported by Hegedus, the source of chirality was bromopentanol **13** obtained from chiral pool reagents.[20] Alcohol **1** (R=OTr) was effortlessly transformed into this synthon using conventional methods (Scheme 3).[21] Other variants are easily prepared via standard methods, including the robust iodopentanol **14**. In the Pattenden synthesis of **2**, which utilized alcohol **15**,[22] the source of this synthon

was naturally derived parasorbic acid, requiring five steps, and effectively restricting studies to the *S* enantiomer. Accordingly, **14** was coupled to 1,3-dithiane, and subjected to selective deprotection to give **15** (Scheme 3).[21]



Scheme 3. Application of **1** in the preparation of (*S*)-(−)-zearalenone synthons[20]

In summary, a new family of enantioselective catalysts has been prepared, and employed to optimize synthesis of important (*S*)-2-pentanol derivatives **1** via catalytic enantioselective methylation of functionalized aldehydes. The merits of the alkylation approach are clear when compared to alternative catalytic methods involving ketone reduction.[23] Catalyst **8d** affords among the highest selectivity ever reported for aldehyde methylation, making application in synthesis a viable prospect. The synthesis and biological evaluation of analogs of **2** will be reported in due course.

Acknowledgements

We thank the Donors of the Petroleum Research Fund (Administered by the American Chemical Society) for financial support of this work (25958-G1, 28706-AC1), Professor Robert S. Phillips and Christian Heiss (University of Georgia) for useful discussions and a gift of SADH, and George R. Martin and John H. Kodjak for some preliminary experiments.

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13. (a) All compounds reported gave satisfactory spectral and analytical data: **7d** ^{13}C NMR (75 MHz, $CDCl_3$) 233.7, 155.8, 129.5, 124.1, 123.5, 120.4, 115.0, 90.3, 85.9, 72.8, 61.1, 50.5, 30.7, 20.5, 14.1, 9.8 and 0.72; following deprotection (alcohol of **8d**) ^{13}C NMR (75 MHz, $CDCl_3$) 234.4, 143.1, 129.8, 128.3, 127.6, 120.3, 115.7, 90.6, 89.1, 73.6, 61.1, 50.9, 30.7, 20.7, 14.3 and 10.1; (b) RX, Et_3N, DMF (44–75%), Dess-Martin (90–96%); (c) RX, Et_3N, DMF (80–97%).
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21. Scheme 3 reagents: (a) TBSOTf, 2,6-lutidine; (b) BCl_3, CH_2Cl_2; (c) CBr_4, PPh_3, K_2CO_3; (d) TBDPSCl; (e) TosCl, NaI; (f) BuLi, 1,3-dithiane; (g) NaH, HMPA.
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