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Design and Evaluation of a Practical Camphor-Based Methyl Ketone Enolate for Highly Stereoselective "Acetate" Aldol Reactions**

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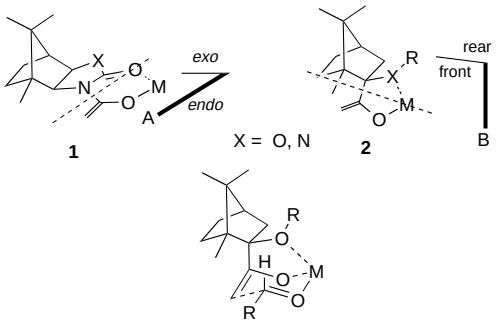
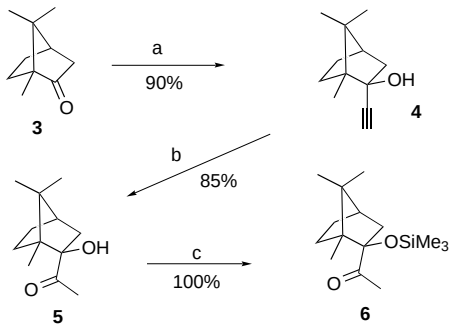
Control of the configuration of newly forming stereogenic carbon atoms in aldol condensation processes has focused enormous efforts over the last two decades.[1] Special attention has been given to the use of chiral enolates derived from carboxylic acids[2] because of the easy final removal of the auxiliary to obtain either β-hydroxy carbonyl or 1,3-dihydroxylic compounds, which are frequently present in natural products.[3] A conceptually different, but in practice equivalent, strategy to access to these fragments lies in the use of enolates derived from chiral α-hydroxy ketones.[4] In this instance, the aldol products, upon oxidative cleavage of the α-ketol moiety, give the desired β-hydroxy carbonyl system.[5] The major drawbacks associated with this strategy are the destruction of the covalently bounded chiral adjuvant at the final stage, and the insufficient stereoselectivity generally attained with α-unsubstituted enolates.[6] Although considerable advances have been made in recent years to overcome this latter limitation by carrying out acetate aldol reactions mediated by both metal enolates bearing chiral ligands and external chiral catalysts,[7] the problem associated with enolates of chiral acetates still remains not well resolved;[8] in all but one case,[4j] the lack of stereoselection in aldol reactions with methyl ketone enolates is specially dramatic.[4b,g,h,i]

We have recently reported on the reaction of *N*-acetyl imide enolates **1** with aldehydes to give the corresponding adducts with modest levels of diastereoselectivity (Scheme 1).[9] In an attempt to take advantage of the stereodifferentiating power of the camphor skeleton more effectively, we designed the new camphor-derived enolate **2**. The conception of **2** has been guided by two major goals: a) to provoke the electrophilic aldehyde to follow a trajectory of approach closer to the camphor skeleton, and b) to force a facial discrimination between the rear side and the sterically more demanding front side of the camphor skeleton, depicted as the half-spaces defined by plane B in Scheme 1,[10] instead of the more commonly used *endo/exo* discrimination across opposite sides of plane A.[11] Accordingly, if one assumes that a chelating metal ion like lithium engages in three-point coordination, a very high diastereoselectivity should be expected through a Zimmerman–Traxler six-membered transition state.[12] From this design the methyl ketone **5**[13] (Scheme 2) is a primary candidate to evaluate the above



Scheme 1. Design of the new chiral methyl ketone enolate **2** by moving the acetyl moiety of **1** nearer to the camphor skeleton. Also shown is the transition state accounting for the aldol reaction of **2**.



Scheme 2. Synthesis of the chiral methyl ketone reagents **5** and **6**: a) HC≡CLi, THF, −78 →room temperature (RT) (*endo:exo* 97:3); b) HgO, H_2SO_4, Me_2CO, reflux; c) TMSO, TfOH cat., RT.

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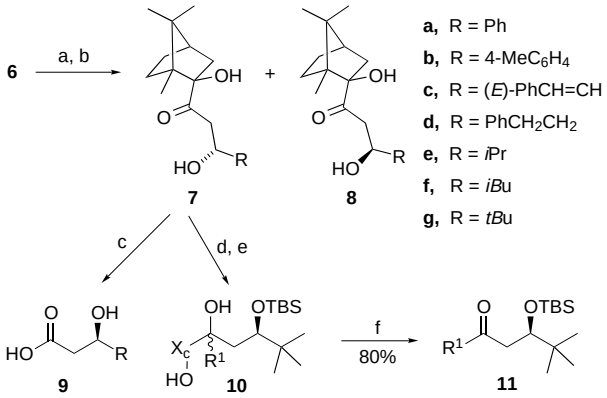
[**] This work was supported by the Government of Navarra (Project O.F. 68/1995) and in part by the Basque Government (Project PI 95/93). Grants to C.L. from the Government of Navarra and the Ministerio de Educación y Cultura (MEC) are acknowledged.

  1433-7851/98/3701-0180 $ 17.50+.50/0

hypothesis. The crystalline **5** was prepared by addition of lithium acetylide to the commercially available (1*R*)-(+)-camphor (**3**) according to the procedure of Midland.[14] The addition proceeded in a 97:3 *endo:exo* ratio from which **4** was isolated in 90% yield after column chromatography. Standard hydration provided **5** [m.p.: 94–95°C, $[\alpha]_D^{25} = -65.6$ ($c = 1.0$ in CH_2Cl_2)] in 85% yield after crystallization from hexane.[15]

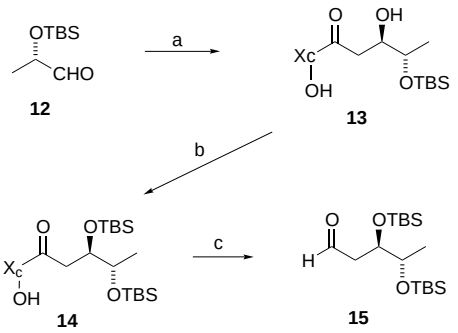
Concordant with our expectations, the corresponding aldol products obtained from the reaction of representative aldehydes with the lithium enolate of **6**, generated from **5** by silylation with *N*-trimethylsilyl-2-oxazolidinone (TMSO)[16] and subsequent treatment with lithium diisopropylamide (LDA), were indeed formed with remarkably high diastereoselectivity (Scheme 3). The diastereomeric ratio of the



Scheme 3. Diastereoselective synthesis of α-unsubstituted β-hydroxy carboxylic acids and ketones: a) LDA (1.2 equiv), THF, -78°C, 0.5 h then RCHO, 3–7 h; b) 1M HCl, MeOH or TBAF (2 equiv), THF, RT, 5 min; c) $NaIO_4$, MeOH/H_2O (2/1), RT or reflux, 12–48 h; d) $ClSiMe_2tBu$, imidazole, DMF, RT, 3 days, 86%; e) R^1MgBr, $CeCl_3$, THF or Et_2O, 0°C, 2 h; f) $Pb(OAc)_4$ (2 equiv), C_6H_6, 5°C, 2 h.

product was unchanged after desilylation to afford the adducts **7**/**8** (typically 95:5, Table 1). The stereochemical assignments for the major products **7** from the reaction with benzaldehyde, isobutyraldehyde, and pivalaldehyde were made by cleavage of the acyloin moiety[5] to afford the corresponding carboxylic acid **9** along with the recovery of the starting camphor (85–90%). The observed optical rotations of these β-hydroxy acids were then compared with published values.[17] In addition, a single-crystal X-ray analysis of the aldol **7g** corroborated the assigned configuration for the adducts. From the data in Table 1 it is evident that the reaction diastereoselectivity is independent of the nature of the aldehyde, showing generality for aromatic, α,β-unsaturated, and linear as well as branched chain aliphatic aldehydes. The excellent diastereoselectivity observed in these reactions is of particular interest in that it provides, through carbonyl addition and subsequent diol cleavage, the basis for an enantioselective synthesis of α-unsubstituted β-hydroxy ketones. For example, using organocerium reagents,[18] we could prepare the carbinols **10** [R^1 = Me, 85%; R^1 = Ph, 90%; R^1 = allyl, 80%],[19] which upon exposure to lead tetraacetate in benzene gave the α-unsubstituted β-silyoxy ketones **11** in good overall yields and essentially in optically pure form.

A further example that illustrates the efficiency of the present system is the reaction of the dianion of **5** with the α-oxy aldehyde **12** (Scheme 4), a chiral aldehyde that shows



Scheme 4. a) **5**, LDA (2.4 equiv), LiCl (6 equiv), THF, -78°C, 4 h, 75%. b) TBDMS-Cl, imidazole, DMF, RT, overnight, 90%. c) $BH_3 \cdot$THF, THF, 0°C, 7 h then $Pb(OAc)_4$ (2 equiv), C_6H_6, 5°C, 2 h, 70%.

essentially no diastereoselection with either methyl acetate or α-silyloxy methyl ketone enolates.[4b, 5b] When **12** was allowed to react with the dianion of **5** in the presence of LiCl, a mixture of diastereomeric aldols was obtained in the ratio 93:7. The major isomer **13** was isolated in 75% yield after column chromatography. A single crystal X-ray analysis of **13** confirmed the assigned configuration for the adduct.[20] Finally, diborane reduction of the keto group in the TBS-protected aldol **14** (TBS = *tert*-butyldimethylsilyl) followed by oxidative workup provided the α-unsubstituted β-silyloxy aldehyde **15** in 70% yield along with the recovery of the starting camphor.

The α-hydroxy methyl ketone enolate developed here helps to fill the existing gap with regard to the usual behavior of α-unsubstituted enolates in diastereoselective aldol reactions and, in addition, enables for the first time the recovery of the starting source of chiral information.

Table 1. Aldol condensation of the lithium enolate of **6** with representative aldehydes.[a]

Aldehyde	t [h]	**7**:**8**[b]	Yield (**7**) [%][c]
C_6H_5CHO	6	96:4	80
4-$CH_3C_6H_4CHO$	7	96:4	67
$C_6H_5CH{=}CHCHO$	6	92:8	80
$C_6H_5CH_2CH_2CHO$	2	95:5	81
i-C_3H_7CHO	3	97:3	67
$(CH_3)_2CHCH_2CHO$	6	96:4	75
$(CH_3)_3CCHO$	6	>98:2	70

[a] Reactions were carried out at -78°C on 0.5 mmol scale by adding a precooled (-78°C) solution of the aldehyde in THF to the lithium enolate of **6** in the same solvent at -78°C. [b] Ratios were determined by both ^{13}C NMR (area of *C*HOH signals of both diastereomers at $\delta = 65-75$) and HPLC analysis of the crude reaction mixture. Diastereomer **8** had the shorter retention time in all HPLC experiments. [c] Yields of **7** after purification of the crude product by column chromatography and separation of diastereomers by HPLC on a Merck LiChrosorb Si 60 column (7 μm) with mixtures of ethyl acetate and hexane as eluent.

Received: June 16, 1997 [Z10552IE]
German version: *Angew. Chem.* **1998**, *110*, 190–192

Keywords: acetylene · aldol reactions · asymmetric synthesis · camphor · methyl ketone

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[{Pt(CN)($C_{10}H_{21}N_4$)}$_6$]: A Luminescent Hexanuclear Platinum(II) Macrocycle Containing Chelating Dicarbene and Bridging Cyanide Ligands**

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Transition metal mediated self-assembly reactions are a versatile strategy for generating supermolecules with appealing structural and spectroscopic properties.[1–6] In this context we are interested in luminescent molecular hosts[7] composed of square-planar platinum(II) complexes as building blocks, since such materials could have applications in host–guest photochemistry and as novel luminescent sensors. Fujita et al.[1] and Stang et al.[5a, b] reported the preparation of tetranuclear platinum(II) compounds with pyridine-based ligands. Here we describe the crystal structure of a novel luminescent hexanuclear platinum(II) macrocycle bearing cyclic dicarbene and bridging cyanide ligands.

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[**] We acknowledge financial support from The University of Hong Kong, the Hong Kong Research Grants Council, and the Croucher Foundation. M. C.-W. C. is grateful for a University Postdoctoral Fellowship from the University of Hong Kong.

  1433-7851/98/3701-0182 $ 17.50+.50/0