ORGANIC LETTERS

2001
Vol. 3, No. 21
3249−3252

Alkylation of Chiral α-Hydroxy Ketones Derived from (1*R*)-(+)-Camphor. An Asymmetric Variant of the Classical Acetylene Route to Carbonyl Compounds

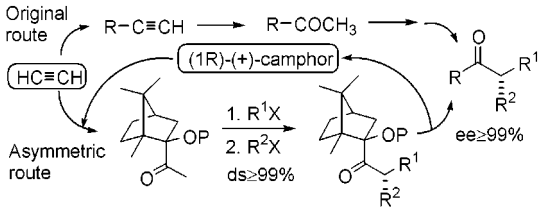
Claudio Palomo,*,† Mikel Oiarbide,† Antonia Mielgo,† Alberto González,‡ Jesús M. García,‡ Cristina Landa,‡ Ainara Lecumberri,‡ and Anthony Linden§

Departamento de Química Orgánica I, Facultad de Química, Universidad del País Vasco, Apdo. 1072, 20080-San Sebastián, Spain, Departamento de Química Aplicada, Universidad Pública de Navarra, Campus de Arrosadía, 31006-Pamplona, Spain, and Organisch-Chemisches Institut der Universität Zürich, Winterthurerstrasse-190, CH-8057, Zürich, Switzerland

qoppanic@sc.ehu.es

Received June 26, 2001

ABSTRACT



The asymmetric version of the traditional route for transforming acetylene into α-branched carbonyl compounds is now feasible for the first time. The method involves the temporary attachment of camphor to acetylene and gives a remarkably high diastereo- and enantioselectivity.

Over the past 30 years, asymmetric alkylation of enolates has become one of the most popular methods for the construction of carbon−carbon bonds.[1] During this time remarkable advances have been made in the development of efficient processes that mainly rely upon the use of chiral auxiliaries.[2] A common feature of these processes is the use as the starting material of a carboxylic acid to which the chiral auxiliary is covalently bonded through the acyl moiety.[3] As a consequence, the problems of chemo- and regioselectivity during enolate formation and alkylation are not applicable. The hydration of terminal alkynes followed by sequential alkylation of the resulting ketones is, on the

† Universidad del País Vasco.
‡ Universidad Pública de Navarra.
§ Organisch-Chemisches Institut der Universität Zürich.

(1) (a) *Stereoselective Synthesis (Houben-Weyl), E21 Vol. 2*; Helmchen, G., Hoffmann, R. W., Mulzer J., Shaumann, E., Eds.; Georg Thieme: Stuttgart, New York, 1996. (b) Fey, P.; Hartwig, W. In ref 1a, pp 969−972. (c) Enders, D. In *Asymmetric Synthesis, Vol. 3B*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; p.275. (d) Enders, D.; Kipphardt, H.; Fey, P. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, pp 403−414. (e) Enders, D.; Klatt, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; p 178. (f) Fey, P. In ref 1a, pp 973−1015. For enantioselective enolate alkylations, see: (g) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439−1457. (h) Hughes, D. L. In *Comprehensive Asymmetric Catalysis III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 1999; pp 1273−1294.

(2) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley: New York, 1995; pp 166−187.

(3) For reviews, see: (a) Rück, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 433−435. (b) Franklin, A. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2451−2465. (c) Regan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1151−1166. (d) Regan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 357−373. (e) Fey, P. In ref 1a, pp 1016−1029. For a recent practical example, see: (f) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

10.1021/ol0163530 CCC: $20.00
Published on Web 09/27/2001

other hand, the classical and most direct route for the transformation of acetylene into α-branched carbonyl compounds. The important advantages of this route are the accessibility of the raw materials needed during the process (only a diversity of alkyl halides would be required for generality) and the minimum number of synthetic steps required to convert commercially available chemicals into somewhat complex small molecules on a large scale. However, although acetylene is one of the least expensive carbon sources, with a worldwide production exceeding 300 000 tons/year,[4] this procedure is inherently nonselective and therefore of limited practical use. Here we present the first asymmetric variant of this process that demonstrates how acetylene and alkyl halides can be transformed into α-branched carbonyl compounds in a chemo-, regio-, and stereoselective way.[5]

The synthetic concept of the approach is outlined in Figure 1 and arises from our earlier reports concerning the use of

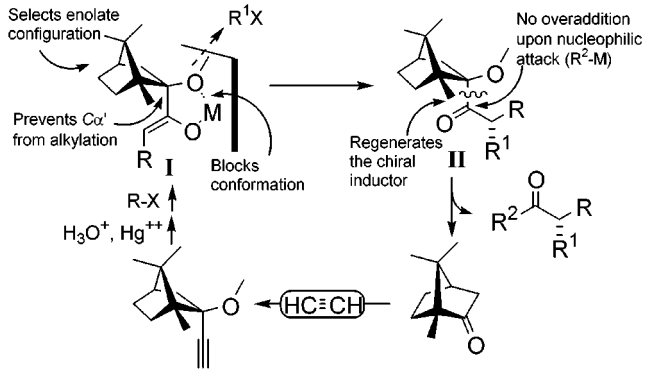
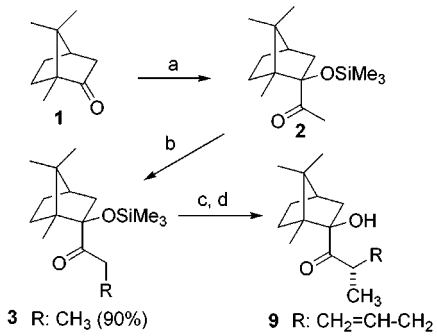


Figure 1. Acetylene and alkyl halides as raw materials for the preparation of carbonyls with an α-stereogenic center. Criteria for working hypothesis: (a) exclusive formation of *Z*-enolates I; (b) pronounced enolate diastereofacial bias; (c) clean release of the auxiliary from II.

(1*R*)-(+)-camphor and acetylene in the "acetate" aldol[6] and Mannich reactions.[7] In our design, acetylene is the elementary source of acetyl that ends up incorporated into the final products. During the alkylation process, (1*R*)-(+)-camphor, in its turn, directs the chemo-, regio-, and diastereoselective incorporation of the two alkyl units in a stepwise fashion and facilitates the optional selective introduction of a third alkyl group (R^2). At the end, camphor is regenerated for reuse, with concomi-tant liberation of the target α-branched carboxylic acid and/or ketone.

To put this design into practice, we succeeded in carrying out the alkylation of **2** under the conditions shown in Scheme 1. Namely, when the lithium enolate of **2** is treated with

Scheme 1. Monoalkylation of Ketone **2** and Methylation of Ketones **4**−**7**[a]



[a] (a) Reference 6. (b) For reactive alkyl iodides: LDA (1.3 equiv), THF, −78 °C, 2 h then R−I (1.3 equiv), −30 °C, 1.5 h. For less reactive aliphatic iodides: LDA (1.3 equiv), THF, −78 °C, 2 h then DMPU (20%), R−I (5−6 equiv), −50 °C, 4 h. (c) LDA (1.5−2.0 equiv), THF, DMPU (20%), −50 °C, 4 h, MeI (1.5 equiv), −30 °C, 1 h. (d) TBAF, THF, rt, 30 min. Yields in parentheses refer to isolated pure compounds. Purity determined by GC analysis and/or analytical HPLC.

reactive alkyl halides, such as methyl iodide, allyl iodide, and benzyl iodide, the reaction proceeds cleanly in THF as solvent to give ketones **3**, **4**, and **5** in 90%, 81%, and 80% isolated yields, respectively, as the exclusive products formed. On the other hand, when primary aliphatic iodides, such as ethyl iodide, propyl iodide, and hexyl iodide were used, the reaction proceeded in the presence of DMPU (20 mol %) to give the monoalkylated products **6**, **7**, and **8** in 83%, 93%, and 73% isolated yields. Remarkably, overalkylation did not occur in any reaction.[8] In line with the observed diastereoface differentiation property of the lithium enolate of **2** in aldol and Mannich reactions, it was found that the alkylation of the alkaline metal enolates of this family of ketones occurs with remarkable diastereoselectivity. For example, the sterically undemanding methylations, which are

(4) For industrial applications of acetylene, see: (a) Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*; VCH: Weinheim, 1997; pp 91−104. (b) Szmant, H. H. *Organic Building Blocks of the Chemical Industry*; John Wiley: New York, 1989; pp 188−264.

(5) For a recent innovative approach to transform alkynes into carbonyls with an α stereogenic center, see: (a) Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832−11833. (b) Spino, C.; Beaulieu, C.; Lafreniere, J. *J. Org. Chem.* **2000**, *65*, 7091−7097.

(6) (a) Palomo, C.; González, A.; García, J. M.; Landa, C.; Oiarbide, M.; Rodríguez, S.; Linden, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 180−182. (b) Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; González, A.; García, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem.* **1999**, *64*, 8193−8200.

(7) Palomo, C.; Oiarbide, M.; González-Rego, M. C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063−1065.

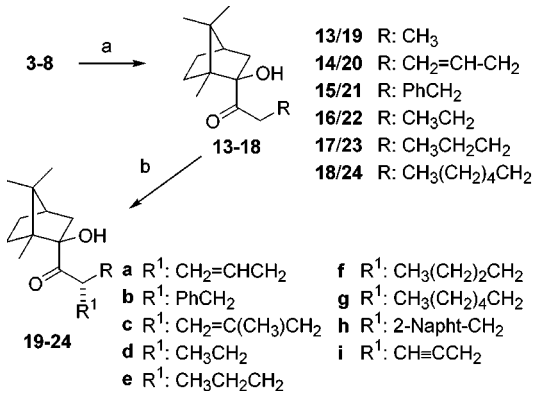
(8) A small amount (2%−4%) of the starting unreacted methyl ketone **2** was isolated in some instances.

(9) For the problem of stereocontrol in enolate methylations, see, for instance: (a) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184−1186. (b) Palomo, C.; Berrée, F.; Linden. A.; Villalgordo, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1861−1862. (c) Boyd, V. A.; Perales, J. B.; Negrete, G. R. *Tetrahedron Lett.* **1997**, *38*, 6631−6634. (d) Abdel-Aziz, A. A.-M.; Okuno, J.; Tanaka, S.; Ishizuka, T.; Matsunaga, H.; Kunieda, T. *Tetrahedron Lett.* **2000**, *41*, 8533−8537.

often difficult to control,[9] proceeded with extremely high efficiency. Thus, ketones **4**−**7** upon exposure to LDA in the presence of DMPU (20 mol %) and subsequent treatment with methyl iodide provided, after desilylation of the resulting intermediates, compounds **9**−**12** in yields of 80−85% and diastereomeric ratios of up to ≥98:2.

On the other hand, the alkylation reactions with other alkyl halides were best accomplished by using the sterically less demanding α′-hydroxy ketones **13**−**18**, Scheme 2. In these

Scheme 2. Asymmetric Alkylations of Ketones **13**−**18**[a]



[a] (a) TBAF, THF, rt, 30−60 min. (b) For reactive alkyl halides: KHMDS (0.5 M in toluene, 2.3−2.5 equiv), THF, −78 °C, 4 h then R^1-Br (2 equiv), THF, −78 → −50 °C, 0.5−1.5 h. For less reactive aliphatic halides: KHMDS (0.5 M in toluene, 2.3−2.5 equiv), DMF, −78 °C, 4 h then R^1-I (3 equiv), −78 °C, 2 h.

instances, the use of potassium as the counterion for enolates was another requirement for optimum results. In this respect, the alkylation of ketones **13**−**18** with reactive alkyl halides proceeded efficiently in THF as solvent, while for less reactive primary aliphatic halides DMF gave superior results,

Table 1. Asymmetric Alkylation of Camphor-Based Ketone Enolates[a]

ketones	R	R^1-X	product[b]	yield, %[c]
4	CH_2=$CHCH_2$	MeI	**9**	81
5	$PhCH_2$	MeI	**10**	85
6	CH_3CH_2	MeI	**11**	78
7	$CH_3CH_2CH_2$	MeI	**12**	80
13	CH_3	CH_2=$CHCH_2Br$	**19a**	92
		$PhCH_2Br$	**19b**	80
		CH_2=$CMeCH_2Br$	**19c**	87
		CH_3CH_2I	**19d**	85[d]
		$CH_3CH_2CH_2I$	**19e**	87[d]
		$CH_3(CH_2)_2CH_2I$	**19f**	75
14	CH_2=$CHCH_2$	$PhCH_2Br$	**20b**	85
15	$PhCH_2$	CH_2=$CHCH_2Br$	**21a**	84
		$CH_3(CH_2)_4CH_2I$	**21g**	70
		2-Naphth-CH_2Br	**21h**	84
16	CH_3CH_2	$CHCCH_2Br$	**22i**	85
17	$CH_3CH_2CH_2$	$PhCH_2Br$	**23b**	80
		CH_3CH_2I	**23d**	86
18	*n*-hexyl	CH_2=$CHCH_2Br$	**24a**	74

[a] All reactions were carried out on a 1−2 mmol scale. For details, see ref 10 and Supporting Information. [b] In all cases, dr ≥ 98:2 as determined by GC using a J&W DB-5 column, unless otherwise mentioned. The validity of this assay is provided by comparison of the chromatograms of **10**/**19b**, **11**/**19d**, and **12**/**19e**. Diastereomers **9**/**19a** were hydrogenated to the corresponding **12**/**19e** for dr determinations. [c] All yields refer to isolated pure products after column chromatography. [d] Traces (∼2%) of *O*-alkylation at the tertiary hydroxyl group was detected by GC analysis of the reaction mixture.

Table 1.[10] In every case, good to excellent yields are attained, and in each case, essentially only one diastereomer is produced. It is also worth noting that, with few exceptions, all of ketone compounds are crystalline, and analytically pure solids of ≥99% de can therefore be isolated by direct crystallization from the crude reaction mixture.

The elucidation of the configuration of the products was achieved by cleavage of the acyloin moiety to afford the corresponding carboxylic acids, along with the recovery of the starting camphor. For example, treatment of **10**, **19b**, and **19d**, Scheme 3, with cerium ammonium nitrate afforded carboxylic acids **25**, **26**, and **27**, respectively, in 90%, 95%, and 90% isolated yields, and in each case the starting camphor was recovered with yields in the range 85−90%.[11] The observed optical rotations of these α-branched carboxylic acids were then compared with published values.[12] In addition, a single-crystal X-ray structure analysis of the alkylated products **19b** and **19c** further corroborated the assigned configuration of the products.[13]

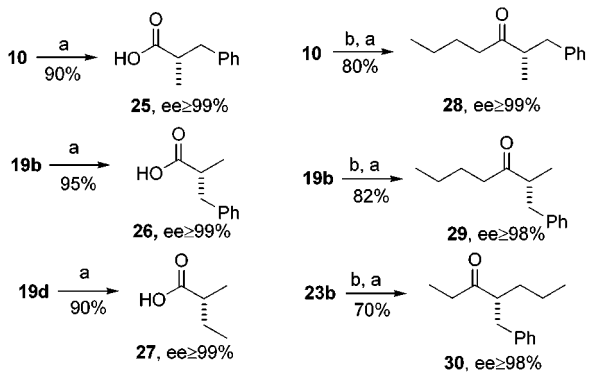
The excellent diastereoselectivity attained with these camphor-based alkyl ketones is also of particular interest in that the reaction provides, through carbonyl addition and

(10) **Alkylation of ketones 13−18 (for reactive alkyl halides):** Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 4.6 mL, 2.3 mmol) was added dropwise to a solution of the starting ketone (1.0 mmol) in dry THF (4.0 mL) at −78 °C under a nitrogen atmosphere, and the mixture was stirred for 4 h at the same temperature. The corresponding bromide (2.0 mmol) was added, and the reaction was allowed to reach −50 °C and was stirred at this temperature until completion (0.5−1.5 h). The reaction was quenched at −50 °C with 5 mL of saturated aqueous NH_4Cl, and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organics were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The alkylated compounds were obtained as white solids or oils, and diastereomeric ratios were determined by gas chromatography at this stage. Purification of the products was effected by flash column chromatography (eluant: ethyl acetate/hexane 1:30). **For less reactive aliphatic alkyl halides:** A solution of the starting ketone (1.0 mmol) in dry DMF (3.0 mL) was added dropwise over a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 5.0 mL, 2.5 mmol) in dry DMF (3.0 mL) at −78 °C, and the mixture was stirred for 4 h at the same temperature. The corresponding iodide (3.0 mmol) was added, and the mixture was stirred for 2 h at this temperature. The reaction was quenched with 5 mL of saturated aqueous NH_4Cl, and the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous phase was extracted twice with Et_2O (15 mL). The combined organic extracts were washed with water (10 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The alkylated products were obtained as white solids or oils. Diatereomeric ratios were determined by gas chromatography. Purification was effected by silica gel flash column chromatography (eluant: ethyl acetate/hexane 1:30).

(11) (1*R*)-(+)-Camphor: Aldrich $[\alpha]^{25}_D = +42.2$ (c = 1.0 in EtOH). Recovered material, $[\alpha]^{25}_D = +41.5$ (c = 1.0 in EtOH).

(12) Observed values: **25** +29.0 (c = 1.0 in $CHCl_3$) [published value +30.4 (c = 1.0 in $CHCl_3$), see: Davies, S. G.; Sanganee, H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 671−674]; **26** −29.5 (c = 1.1 in $CHCl_3$) [published value −25.1 (neat), see: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739]; **27** −16.0 (c = 1.0 in CH_2Cl_2) [published value for the (*S*)-isomer +19 (neat) [Aldrich catalog]].

Scheme 3. Enantioselective Synthesis of α-Branched Carboxylic Acids and Ketones[a]



[a] (a) $(NH_4)_2Ce(NO_3)_6$ (3 equiv), CH_3CN/H_2O, 0 °C, 1 h. (b) RLi (3 equiv), THF, −78 → 0 °C, 1 h.

subsequent diol cleavage, access to α-branched alkyl ketones.[1e,14] Under optimized conditions (−78 → 0 °C), the reaction proceeds with 3 equiv of the respective alkyllithium within about 1 h to give, after diol cleavage, ketones **28**, **29**, and **30** in good yields and essentially without racemization of the α-stereocenter. This transformation formally represents a perfectly regiocontrolled alkylation of nearly symmetrical ketones.[15,16] Importantly, simply by changing the alkylation sequence of the process, access to either one of the enantiomeric forms of the final carbonyl compound (i.e. **25**/**26**, **28**/**29**) would be possible by starting from just a single chiral unit, the methyl ketone **2**. Therefore, a wide variety of α-branched carbonyl compounds with the desired α-configuration can easily be prepared from acetylene and alkyl halides, which are the only organic raw materials that are consumed during the reaction.

Acknowledgment. This work was finantially supported by Universidad del País Vasco, Gobierno Vasco, and by MEC (PB 98-0549). Grants to A.S. and M.C.G. from Gobierno Vasco, to C.L. from MEC, and to A. Lecumberri from UPNA are acknowledged.

Supporting Information Available: Experimental procedures for alkylation reactions, desilylation, and cleavage to carboxylic acids and ketones; characterization data for compounds **3**, **10**, **13**, **19b**, **19d**, **23b**; ORTEP diagrams of **19b** and **19c**; and representative ^1H, ^{13}C, and MS spectra and GC and HPLC chromatograms of compounds **26**, **27**, **28**, **29**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0163530

(13) Crystallographic data (excluding structure factors) for the structures **19b** and **19c** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as suplemmentary publication numbers CCDC-161732 and 161733, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (+44) 1223 336−033; e-mail deposit@ccdc.cam.ac.uk).

(14) For a recent example, see: Oppolzer, W.; Darcel, C.; Rochet, P.; Rosset, S.; deBrabander, J. *Helv. Chim. Acta* **1997**, *80*, 1319−1337.

(15) For the problems associated with the alkylation of open-chain ketones, see: ref 2, p 168.

(16) The enantiomeric purity of carboxylic acids **25**, **26**, and **27** was determined by HPLC analyses of their methyl esters using a ChiralCel OB-H column and hexanes as the eluant (flow 0.5 mL/min). The same method was applied for the determination of the enantiomeric purity of ketones **28**, **29**, and **30**, and it was confirmed by comparison of the chromatograms with those corresponding to racemic products.