Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2907–2909

TETRAHEDRON LETTERS

Preparation of chiral annulated indenes derived from nopinone, verbenone and menthone

Ronald L. Halterman* and Lisa D. Crow*

Department of Chemistry and Biochemistry, University of Oklahoma, 620 Parrington Oval, Norman, OK 73019, USA

Received 31 January 2003; revised 12 February 2003; accepted 13 February 2003

Abstract—A three-step procedure for the synthesis of chiral annulated indenes is described in which nopinone, verbenone and menthone are converted to their enolate form, alkylated with 2-bromomethylbromobenzene, ring-closed with $CrCl_2$/cat. $NiCl_2$ and dehydrated with catalytic acid. © 2003 Published by Elsevier Science Ltd.

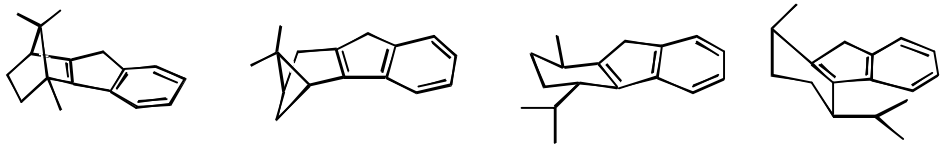
1. Introduction

Chiral indenes are especially desirable as ligands for the preparation of indenyl- and bisindenylmetal complexes.[1] Although a good variety of methods for the preparation of chiral monosubstituted indenes exist,[2] relatively few methods have been developed for the preparation of chiral annulated indenes. These methods include thermally-induced rearrangements of spiroannulated indenes[3] and Nazarov cyclizations of phenyl substituted allylic alcohol derivatives of (1*R*)-(+)-nopinone and (1*S*)-(−)-verbenone.[4] Previously, we reported the development of a methodology that allowed for three-step synthesis of 2,3-disubstituted indenes from 2-bromobenzyl bromide and a variety of ketones using enolate alkylation, the Nozaki–Takai–Hiyama–Kishi Ni(II)/Cr(II)-mediated coupling of aryl bromides with ketone carbonyls and dehydration of the subsequently formed benzylic alcohol.[5] Here, we report the application of this method to the synthesis of chiral annulated indenes **1**–**3** from (1*R*)-(+)-camphor, (1*R*,5*S*)-(+)-nopinone, and (−)-menthone and 2-bromobenzyl bromide in moderate to very good yields.[6]

2. Results and discussion

In the synthesis of the (1*R*)-(+)-camphor annulated indene **1**, good selectivity was achieved by alkylating the lithium enolate of camphor at room temperature with an excess of 2-bromobenzyl bromide. After removal of unalkylated camphor by filtration, distillation was used to remove remaining 2-bromobenzyl bromide and the product **5** was isolated as a colorless oil. The tethered ketone was easily cyclized with excess $CrCl_2$ and catalytic $NiCl_2$ in DMF at 125°C overnight. After workup, the resultant alcohol was quantitatively converted to the methanesulfonate ester and eliminated using excess triethylamine in refluxing benzene to give indene **1** as a brown oil. After purification by chromatography indene **1** was isolated in 54% overall yield for the alkylation, coupling and elimination reactions.

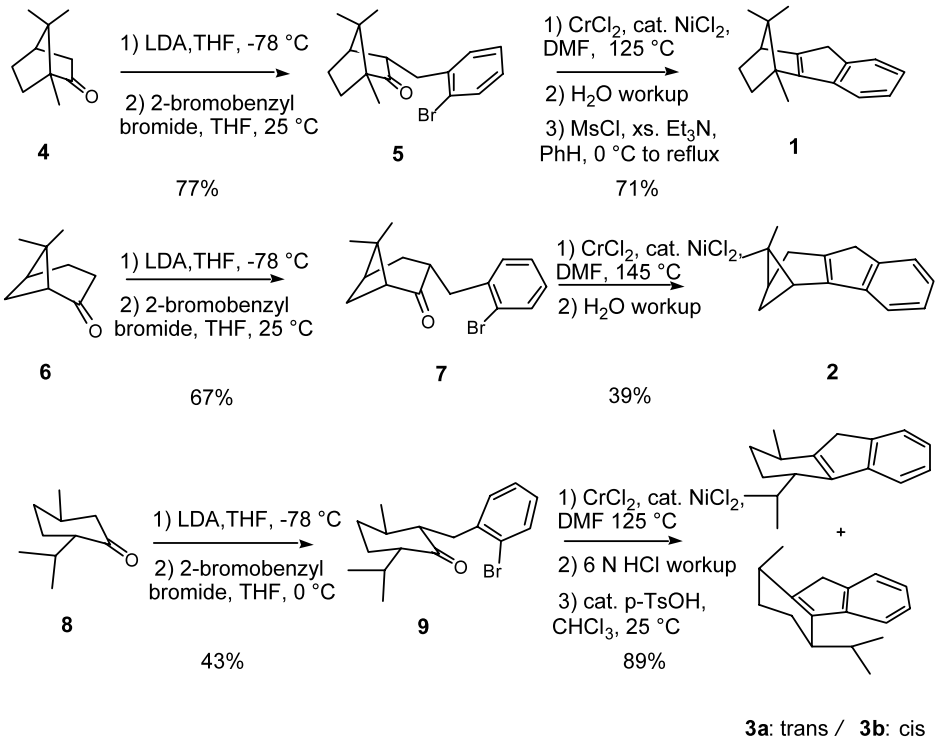
Alkylation of the (1*R*,5*S*)-(+)-nopinone lithium enolate with 2-bromobenzyl bromide under the same conditions proceeded regio- and stereoselectively with moderate to good yields. The tethered ketone **7** was purified by recrystallization as a white solid from hexanes. The



1 **2** **3a**: trans **3b**: cis

* Corresponding authors. Tel.: 1-405-325-4811; fax: 1-405-325-6111; e-mail: rhalterman@ou.edu

0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4039(03)00430-1



$CrCl_2$ promoted, $NiCl_2$ catalyzed coupling of ketone **7** would only proceed at the elevated temperatures (145°C) over a prolonged time period (80 h), so that the dehydrated product was isolated upon aqueous workup. The nopinanyl annulated indene **2**, a yellow oil, was easily separated by column chromatography from the side product (yellow oil, 20%), a diol resulting from intermolecular carbonyl addition, for a yield of 39%.

The alkylation of the enolate of (−)-menthone with 2-bromobenzylbromide was performed at 0°C to give substituted menthone **9** as a single stereoisomer in moderate yield after purification. The chromium-promoted coupling proceeded at 125°C with very good yield (89%). Unfortunately, these condit2ions caused epimerization of the isopropyl group. When a 6N HCl workup was used to dehydrate the alcohols, a 1:1 diastereomeric mixture of *cis* and major isomers and **3b** was obtained. After stirring in $CHCl_3$ with cat. TsOH at room temperature, the menthyl annulated indene mixture isomerized to an improved ratio of 2:1. The isomers were inseparable by preparative chromatography.

In summary, we have synthesized chiral annulated indenes from (1*R*)-(+)-camphor, (1*R*,5*S*)-(+)-nopinone, and (−)-menthone using a modification of the Nozaki–Takai–Hiyama–Kishi Ni(II)/Cr(II)-mediated coupling. This facile synthesis of chiral annulated indenes should now enable a more extensive investigation of the chemistry of chiral indenylmetal complexes—work that is now in progress in our laboratories.

Acknowledgements

We thank the Oklahoma Center for the Advancement of Science and Technology in cooperation with Chevron Phillips Chemical Company, LP (AR7-11) and the National Science Foundation (CHE-0091770) for support of this work.

References

1. (a) Halterman, R. L. In *Metallocenes*; Togni, A.; Halterman, R. L., Eds.; Wiley-VCH: Weinheim, 1998; pp. 455–544; (b) Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965–994.
2. (a) Erker, G.; Aulbach, M.; Krueger, C.; Werner, S. *J. Organomet. Chem.* **1993**, *450*, 1–7; (b) Schumann, H.; Stenzel, O.; Girgsdies, F. *Organometallics* **2001**, *20*, 1743–1751; (c) Halterman, R. L.; Fahey, D. R.; Bailly, E. F.; Docter, D. W.; Stenzel, O.; Shipman, J. L.; Khan, M. A.; Dechert, S.; Schumann, H. *Organometallics* **2000**, *19*, 5464–5470.
3. Chen, Z.; Halterman, R. L. *J. Am. Chem. Soc.* **1992**, *114*, 2276–2277.
4. (a) Liu, C.; Sowa, J. R., Jr. *Tetrahedron Lett.* **1996**, *37*, 7241–7244; (b) Rupert, K. C.; Liu, C. C.; Nguyen, T. T.; Whitener, M. A.; Sowa, J. R., Jr. *Organometallics* **2002**, *21*, 144–149.
5. (a) Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445–7448; (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284; (c) Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343–350; (d) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646; (e) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386–5387; (f) Stamos, D. P.; Sheng, C.; Chen, S. S.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6355–6358.
6. The preparation of tethered ketones and indenes followed the general synthetic procedure given in: Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445–7448 with any

modifications reported here in the results and discussion section. The (1*R*,5*S*)-(+)-nopinone was prepared by ozonolysis of (−)-β-pinene following a procedure described in: Boger, D. L.; Mullican, M. D.; Hellberg, M. R.; Patel, M. *J. Org. Chem.* **1985**, *50*, 1904–1911. Compounds **1**–**3**, **5**, **7**, and **9** were characterized by spectroscopic methods. Selected data for these compounds are given here.

5: MS (EI, 70 eV, rel. %) 321 (4, M^+), 241 (100, loss of $Br^\bullet$), 95 (13); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (d, J=7.5 Hz, 1H), 7.24 (m, 2H), 7.06 (ddd, J=3.0, 6.0, 7.5 Hz, 1H), 3.20 (dd, J=14.0, 4.5 Hz, 1H), 2.84 (ddd, J=10.0, 4.5, 4.0 Hz, 1H), 2.71 (dd, J=14.0, 10.0 Hz, 1H), 1.95 (br. dd, J=3.5, 4.0 Hz, 1H), 1.80–1.66 (m, 3H), 1.40 (m, 1H), 0.98 (s, 3H), 0.93 (s, 3H), 0.87 (s, 3H).

1: MS (EI, 70 eV, rel. %) 224 (90, M^+), 181 (100), 179 (76), 165 (69), 91 (16); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (d, J=7.5 Hz, 1H), 7.30 (d, J=7.5 Hz, 1H), 7.19 (dd, J=7.5, 7.5 Hz, 1H), 7.04 (dd, J=7.5, 7.5 Hz, 1H), 3.31 (d, J=23.0 Hz, 1H), 3.07 (d, J=23.0 Hz, 1H), 2.60 (d, J=3.5 Hz, 1H), 1.97 (dddd, J=12.0, 8.5, 3.5, 3.5 Hz, 1H), 1.71 (br. ddd, J=12.0, 8.5, 3.5 Hz, 1H), 1.39 (s, 3H), 1.09 (ddd, J=12.0, 9.0, 3.5 Hz, 1H), 0.91 (ddd, J=12.0, 9.0, 3.5 Hz, 1H), 0.87 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.3 (C), 151.7 (C), 147.3 (C), 142.3 (C), 126.2 (CH), 124.4 (CH), 123.0 (CH), 118.4 (CH), 61.0 (C), 53.4 (C), 52.4 (CH), 34.9 (CH_2), 33.5 (CH_2), 26.4 (CH_2), 20.5 (CH_3), 19.8 (CH_3), 12.5 (CH_3).

7: Mp=117–120°C; MS (EI, 70 eV, rel. %) 307 (12, M^+), 227 (100, loss of $Br^\bullet$), 171 (26), 157 (21), 95 (20); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, J=8.0 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.21 (dd, J=8.0, 8.0 Hz, 1H), 7.05 (dd, J=8.0, 8.0 Hz, 1H), 3.60 (dd, J=13.5, 4.5 Hz, 1H), 3.01 (ddd, J=10.0, 8.5, 4.5 Hz, 1H), 2.62 (dd, J=5.0, 5.0 Hz, 1H), 2.60 (dd, J=13.5, 10.0 Hz, 1H), 2.42 (ddd, J=10.0, 5.0, 5.0 Hz, 1H), 2.19 (ddd, J=4.5, 5.0, 5.0 Hz, 1H), 1.99 (ddd, J=13.5, 10.0, 4.5 Hz, 1H), 1.68 (d, J=10.0 Hz, 1H), 1.62 (dd, J=13.5, 8.5 Hz, 1H), 1.31 (s, 3H), 0.79 (s, 3H).

2: MS (EI, 70 eV, rel. %) 210 (100, M^+), 195 (8), 167 (13), 165 (10); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, J=7.5 Hz, 1H), 7.22 (dd, J=7.5, 7.5 Hz, 1H), 7.15 (d, J=7.5 Hz, 1H), 7.07 (dd, J=7.5, 7.5 Hz, 1H), 3.29 (d, J=23.0 Hz, 1H), 3.24 (d, J=23.0 Hz, 1H), 2.77 (dd, J=5.5, 5.5 Hz, 1H), 2.69 (dd, J=18.0, 3.0 Hz, 1H), 2.62 (dd, J=18.0, 3.0 Hz, 1H), 2.61 (ddd, J=9.0, 5.5, 5.5 Hz, 1H), 2.29 (dddd, J=3.0, 3.0, 5.5, 5.5 Hz, 1H), 1.42 (s, 3H), 1.33 (d, J=9.0 Hz, 1H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.2 (C), 145.2 (C), 144.4 (C), 137.8 (C), 126.2 (CH), 123.8 (CH), 123.5 (CH), 117.4 (CH), 42.0 (CH), 40.7 (C), 39.43 (CH), 38.9 (CH_2), 33.1 (CH_2), 31.6 (CH_2), 26.8 (CH_3), 21.6 (CH_3).

9: MS (EI, 70 eV, rel. %) 323 (13, M^+), 243 (100, loss of $Br^\bullet$), 187 (53), 159 (15), 131 (18), 107 (28); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (d, J=7.5 Hz, 1H), 7.42 (d, J=7.5 Hz, 1H), 7.15 (dd, J=7.5, 7.5 Hz, 1H), 6.98 (dd, J=7.5, 7.5 Hz, 1H), 3.11 (dd, J=13.5, 9.5 Hz, 1H) 2.83 (dd, J=13.5, 3.0 Hz, 1H), 2.52 (ddd, J=3.0, 9.5, 12.0 Hz, 1H), 2.08 (m, 1H), 2.04 (m, 1H), 2.00 (dsept, J=6.5, 6.5 Hz, 1H), 1.88 (dddd, J=5.5, 5.5, 5.5, 13.5 Hz, 1H), 1.67 (dddq, J=12.0, 11.5, 4.0, 7.0 Hz, 1H), 1.52 (dddd, J=13.0, 12.0, 12.0, 4.0 Hz, 1H), 1.31 (dddd, J=13.0, 11.5, 11.5, 4.0 Hz, 1H), 1.21 (d, J=7.0 Hz, 3H), 0.81 (d, J=6.5 Hz, 3H), 0.76 (d, J=6.5 Hz, 3H). **3a**/**3b**: IR (thin film) 3045, 3000, 2940, 1595, 1450; MS (EI, 70 eV, rel. %) 226 (100, M^+), 211 (14), 183 (70), 167 (11), 155 (22), 141 (23); **3a** (*trans* isomer) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (d, J=7.5 Hz, 1H), 7.36 (d, J=7.5 Hz, 1H), 7.22 (dd, J=7.5, 7.5 Hz, 1H), 7.10 (dd, J=7.5, 7.5 Hz, 1H), 3.35 (dd, J=3.0, 23.0 Hz, 1H), 3.28 (d, J=23.0 Hz, 1H), 2.69 (m, 1H), 2.55 (m, 1H), 2.53 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.64 (m, 1H), 1.28 (m, 1H), 1.16 (d, J=7.0 Hz, 3H), 1.06 (d, J=7.0 Hz, 3H), 0.72 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.9 (C), 146.2 (C), 143.4 (C), 138.5 (C), 126.0 (CH), 123.6 (CH), 123.5 (CH), 119.9 (CH), 39.5 (CH), 38.8 (CH_2), 31.3 (CH), 30.9 (CH_2), 29.7 (CH), 21.7 (CH_3), 21.7 (CH_2), 21.4 (CH_3), 17.9 (CH_3).