Influence of Geminal Disubstitution on Samarium Diiodide Induced Reductive Cyclizations of γ-Aryl Ketones

André Niermann, Hans-Ulrich Reissig*

Freie Universität Berlin, Institut für Chemie und Biochemie, Takustr. 3, 14195 Berlin, Germany
Fax +49(30)83855367; E-mail: hans.reissig@chemie.fu-berlin.de

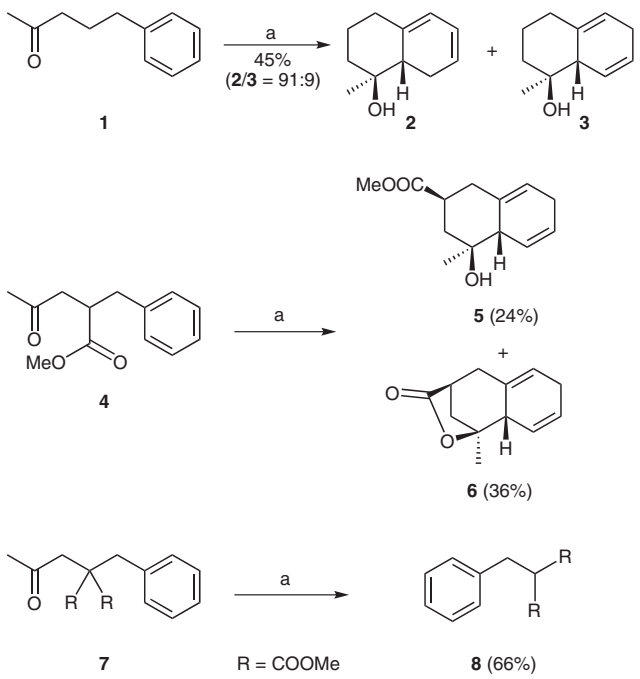
Received 23 November 2010

Abstract: Geminal disubstitution at the alkyl chain of γ-aryl ketones significantly influences the efficacy of samarium diiodide induced cyclizations providing significantly higher yields. β,β-Disubstituted aryl ketones **11a–e** and γ,γ-disubstituted aryl ketone **14** could be converted into the corresponding hexahydronaphthalene derivatives in good yields. On the other hand, α,α-disubstituted ketone **9** only gave the secondary alcohol **10** along with recovered starting material. Aryl ketones containing substituents with heteroatoms could also be cyclized in high yields and substrates such as **11d** with sterically demanding cyclic substituents efficiently afforded spiro compounds.

Key words: samarium diiodide, cyclization, geminal disubstitution, γ-aryl ketone, hexahydronaphthalene

Samarium diiodide has become one of the most efficient reagents in organic syntheses for the formation of new carbon–carbon bonds.[1] In our group it was used to promote intramolecular reductive ketyl–aryl couplings furnishing functionalized dearomatized products with often very high diastereoselectivity.[1h] In this manner, ketones with (substituted) phenyl,[2,3] naphthyl,[4] aniline,[5] indole, pyrrole,[6] and quinoline[7] moieties in γ-position were successfully employed as precursors in this reductive cyclization reaction. Recently, we reported the shortest formal total synthesis of strychnine applying a samarium diiodide cascade reaction as crucial step.[6f]

Simple γ-aryl ketones as substrates react with samarium diiodide to afford hexahydronaphthalene derivatives in a 6-*trig*-cyclization with excellent diastereoselectivity. Thus, treatment of γ-phenyl ketone **1** with two equivalents of samarium diiodide in the presence of HMPA and *tert*-butanol in THF furnished 1,3-diene **2** and its isomer 1,4-diene **3** in 45% yield (Scheme 1).[2g] Ketone **4**, bearing a methoxycarbonyl group as β-substituent of the spacer unit, gave the corresponding hexahydronaphthalene derivative **5** along with γ-lactone **6** in a slightly higher cyclization yield of 60%.[2a] Since it is well established that geminal dialkyl substituents have a favorable influence on numerous cyclization reactions,[8] we investigated the effect of such substitution patterns on the samarium diiodide induced reductive cyclization. Unfortunately, the easily accessible ketone **7** with two methoxycarbonyl substituents was not a suitable model substrate. It did not provide the desired cyclization product under standard conditions, but fragmentation product **8** which is probably the result of a reductive elimination of the acetone subunit.[9] Our results with precursors that cannot undergo this undesired fragmentation process are disclosed here.



Scheme 1 Samarium diiodide induced conversion of γ-aryl ketones with different substitution patterns. *Reagents and conditions*: (a) SmI_2 (2.2–2.4 equiv), HMPA (18 equiv), *t*-BuOH (2 equiv), THF, r.t.

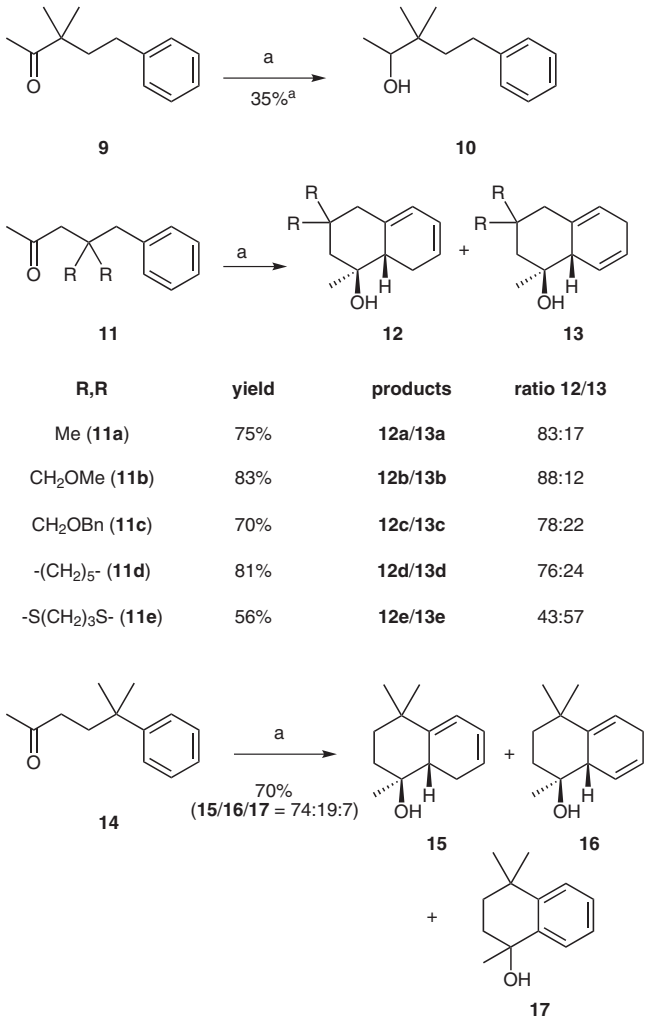
We started our investigation with dimethyl substituted aryl ketones **9**,[10] **11a**,[11] and **14**,[12] bearing the groups in α-, β-, or γ-position, respectively (Scheme 2). Attempts to cyclize ketone **9** failed. Instead of the expected bicyclic product most of the substrate was recovered along with a small amount of secondary alcohol **10** as simple reduction product. The conversion of this ketone was probably unsuccessful due to the high steric hindrance at the reacting carbonyl group.[1h,9] Apparently, the generated samarium ketyl is strongly hampered to approach the phenyl ring and hence cyclization does not occur.[13]

Gratifyingly, ketones **11a** and **14** led to the desired cyclization products in good yields under standard conditions,[14] although mixtures of the conjugated 1,3-dienes **12a/15** and their 1,4-diene isomers **13a/16** were isolated (Scheme 2).[15] In the case of **14**, tetralin derivative **17** was

SYNLETT 2011, No. 4, pp 0525–0528
Advanced online publication: 02.02.2011
DOI: 10.1055/s-0030-1259526; Art ID: G36010ST

also obtained in small amount. It is assumed that this compound is generated by oxidative rearomatization of **15** or **16** during workup or purification. Compared to the cyclization of parent system **1**, conversion of the dimethyl substituted ketones **11a** and **14** proceeded with a significantly increased cyclization yield.[16]

We then explored the influence of other β-positioned substituents in precursors **11**. All substrates **11b–e** furnished the expected products **12** and **13** in satisfying to very good yields under standard conditions of the samarium diiodide induced cyclization reaction. Oxygen-containing substituents in **11b**,**c** were fully compatible with the method employed. In fact, bis(methoxymethyl)-substituted ketone **11b** provided the highest cyclization yield of all examples. Sterically demanding cyclic systems such as **11d** also underwent smooth conversion into the spiro compounds **12d** and **13d**. Furthermore, 1,3-dithiane derivative **11e** could be converted into the corresponding cyclization products **12e** and **13e** in moderate yield.



R,R	yield	products	ratio 12/13
Me (**11a**)	75%	**12a/13a**	83:17
CH_2OMe (**11b**)	83%	**12b/13b**	88:12
CH_2OBn (**11c**)	70%	**12c/13c**	78:22
$-(CH_2)_5-$ (**11d**)	81%	**12d/13d**	76:24
$-S(CH_2)_3S-$ (**11e**)	56%	**12e/13e**	43:57

Scheme 2 Conversion of geminal disubstituted γ-aryl ketones with samarium diiodide. [a] Yield based on recovered starting material. *Reagents and conditions*: (a) SmI_2 (3 equiv), HMPA (18 equiv), *t*-BuOH (2 equiv), THF, r.t.

In summary, we could demonstrate that geminal disubstitution at the alkyl chain of γ-aryl ketones significantly increases the yields of samarium diiodide induced cyclizations, given that substitution is not positioned to close to the carbonyl function as in the case of α,α-disubstituted derivative **9**. These successful cyclizations allow a fast entry to highly substituted hexahydronaphthalene derivatives including new spiro compounds. Our model studies should allow an improved design of samarium diiodide induced cyclizations and hence increase the synthetic value of this approach to polycyclic compounds.

Acknowledgment

The authors thank the Deutsche Forschungsgemeinschaft and the Bayer Schering Pharma AG for support. We gratefully acknowledge the help of Dr. R. Zimmer during preparation of this manuscript.

References and Notes

(1) For selected reviews, see: (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (b) Khan, F. A.; Zimmer, R. *J. Prakt. Chem.* **1997**, *339*, 101. (c) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (d) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (e) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (f) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (g) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (h) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 422. (i) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607. (j) Rudkin, I. M.; Miller, L. C.; Procter, D. J. *Organomet. Chem.* **2008**, *34*, 19. (k) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7140; *Angew. Chem.* **2009**, *121*, 7276. (l) Procter, D. J.; Flowers, R. A. II; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; RSC: Cambridge, **2010**. (m) Beemelmanns, C.; Reissig, H.-U. *Chem. Soc. Rev.* **2011**, *40*, in press; DOI: 10.1039/C0CS00116C.

(2) (a) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **1999**, *38*, 789; *Angew. Chem.* **1999**, *111*, 874. (b) Nandanan, E.; Dinesh, C. U.; Reissig, H.-U. *Tetrahedron* **2000**, *56*, 4267. (c) Berndt, M.; Reissig, H.-U. *Synlett* **2001**, 1290. (d) Ohno, H.; Maeda, S.-i.; Okumura, M.; Wakayama, R.; Tanaka, T. *Chem. Commun.* **2002**, 316. (e) Ohno, H.; Wakayama, R.; Maeda, S.-i.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909. (f) Ohno, H.; Okumura, M.; Maeda, S.-i.; Iwasaki, H.; Wakayama, R.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 7722. (g) Wefelscheid, U. K.; Berndt, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2008**, 3635.

(3) For related ketyl–aryl couplings, see: (a) Kise, N.; Suzumoto, T.; Shono, T. *J. Org. Chem.* **1994**, *59*, 1407. (b) Schmalz, H.-G.; Siegel, S.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2383; *Angew. Chem.* **1995**, *107*, 2597. (c) Shiue, J.-S.; Lin, M.-H.; Fang, J.-M. *J. Org. Chem.* **1997**, *62*, 4643. (d) Heimann, J.; Schäfer, H. J.; Fröhlich, R.; Wibbeling, B. *Eur. J. Org. Chem.* **2003**, 2919.

(4) (a) Berndt, M.; Hlobilova, I.; Reissig, H.-U. *Org. Lett.* **2004**, *6*, 957. (b) Aulenta, F.; Berndt, M.; Brüdgam, I.; Hartl, H.; Sörgel, S.; Reissig, H.-U. *Chem. Eur. J.* **2007**, *13*, 6047. (c) Wefelscheid, U. K.; Reissig, H.-U. *Adv. Synth. Catal.* **2008**, *350*, 65. (d) Wefelscheid, U. K.; Reissig, H.-U. *Tetrahedron: Asymmetry* **2010**, *21*, 1601.

(5) (a) Gross, S.; Reissig, H.-U. *Synlett* **2002**, 2027. (b) Kumaran, R. S.; Brüdgam, I.; Reissig, H.-U. *Synlett* **2008**, 991.
(6) (a) Gross, S.; Reissig, H.-U. *Org. Lett.* **2003**, *5*, 4305. (b) Blot, V.; Reissig, H.-U. *Synlett* **2006**, 2763. (c) Blot, V.; Reissig, H.-U. *Eur. J. Org. Chem.* **2006**, 4989. (d) Beemelmanns, C.; Reissig, H.-U. *Org. Biomol. Chem.* **2009**, *7*, 4475. (e) Beemelmanns, C.; Blot, V.; Gross, S.; Lentz, D.; Reissig, H.-U. *Eur. J. Org. Chem.* **2010**, 2716. (f) Beemelmanns, C.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2010**, *49*, 8021; *Angew. Chem.* **2010**, *122*, 8195. (g) For a related electrochemical cyclization, see: Kise, N.; Mano, T.; Sakurai, T. *Org. Lett.* **2008**, *10*, 4617.
(7) Aulenta, F.; Wefelscheid, U. K.; Brüdgam, I.; Reissig, H.-U. *Eur. J. Org. Chem.* **2008**, 2325.
(8) (a) For a recent review, see: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735. (b) Mitchell, L.; Parkinson, J. A.; Percy, J. M.; Singh, K. *J. Org. Chem.* **2008**, *73*, 2389. (c) Karaman, R. *Tetrahedron Lett.* **2009**, *50*, 6083. (d) Kim, H.; Park, Y.; Hong, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 7577; *Angew. Chem.* **2009**, *121*, 7713.
(9) Berndt, M. *Dissertation*; Freie Universität Berlin: Germany, **2003**.
(10) Compound **9** was synthesized in a two-step procedure: 1. ethyl isobutyrate, phenethyl iodide, LDA, HMPA, THF, –78 °C; 2. $TMSCH_2Li$, pentane, 0 °C then MeOH, 55% (2 steps). For the second step, see: Demuth, M. *Helv. Chim. Acta* **1978**, *61*, 3136.
(11) Conjugate addition of a benzyl cuprate to mesityl oxide furnished compound **11a** in low yield: BnMgCl, CuCN, $BF_3{\cdot}OEt_2$, mesityl oxide, Et_2O, –78 °C, 15%.
(12) Mahmud, S. A.; Ansell, M. F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2789.
(13) The samarium ketyl is very likely in equilibrium with ketone **9** which was re-isolated. Reduction of the ketyl and subsequent protonation furnishes **10**.
(14) **General Procedure for Samarium Diiodide Induced Cyclizations of Aryl Ketones**
HMPA (18 equiv) was added to a previously prepared stock solution of SmI_2 in THF (0.1 M, 3 equiv) under argon, and the solution was stirred for 20 min. During this time the solution turned from dark blue to dark violet. In a separate flask, the substrate (1 equiv) and *t*-BuOH (2 equiv) were dissolved in THF (10 mL) under argon. Argon was bubbled through the solution for 20 min. The substrate solution was then transferred with a syringe to the samarium diiodide solution. The mixture was stirred at r.t. until the color changed from violet to grey. Saturated aq $NaHCO_3$ solution was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3×). The combined organic layers were washed with H_2O and brine, dried with $MgSO_4$, and the solvent was removed under reduced pressure to give the crude product, which still contained small amounts of HMPA. Flash chromatography on Al_2O_3 (activity grade 3) yielded the cyclization products.
(15) **Cyclization of 11a**
According to the general procedure, the SmI_2 solution in THF (15.8 mL, 1.58 mmol), HMPA (1.66 mL, 9.47 mmol), **11a** (0.100 g, 0.53 mmol), and *t*-BuOH (0.078 g, 1.05 mmol) afforded after purification by flash chromatography (hexane–EtOAc, 9:1) compounds **12a** and **13a** as a 83:17 mixture in 75% yield (76 mg).
Spectroscopic Data for (1*S,8a*S**)-1,3,3-Trimethyl-1,2,3,4,8,8a-hexahydronaphthalen-1-ol (12a)**
^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.93, 0.96. 1.26* (3 s, 3 H each, CH_3), 1.28* (br s, 1 H, OH), 1.50 (d, *J* = 13.4 Hz, 1 H, 2-H), 1.62 (dd, *J* = 2.2, 13.4 Hz, 1 H, 2-H), 1.88 (dd, *J* = 2.2, 12.6 Hz, 1 H, 4-H), 2.03 (d, *J* = 12.6 Hz, 1 H, 4-H), 2.23 (dd, *J* = 3.5, 13.0 Hz, 1 H, 8a-H), 2.49 (tdd, *J* = 3.1, 13.0, 19.5 Hz, 1 H, 8-H), 2.57 (m, 1 H, 8-H), 5.54 (tddd, *J* = 0.9, 3.1, 8.6, 9.5 Hz, 1 H, 7-H), 5.58–5.60 (m, 1 H, 5-H), 5.67 (dddd, *J* = 1.3, 3.1, 5.4, 9.5 Hz, 1 H, 6-H) ppm; * overlapping signals. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 22.4 (t, C-8), 23.2, 26.6 (2 q, CH_3), 32.8 (s, C-3) 33.9 (q, CH_3), 46.9 (d, C-8a), 48.7 (t, C-4), 55.9 (t, C-2), 74.9 (s, C-1), 118.9, 122.2, 123.5 (3 d, C-5, C-6, C-7), 136.5 (s, C-4a) ppm.
Spectroscopic Data for (1*S,8a*S**)-1,3,3-Trimethyl-1,2,3,4,6,8a-hexahydronaphthalen-1-ol (13a)**
^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.90, 0.98, 1.12 (3 s, 3 H each, CH_3), 1.52 (br s, 1 H, OH), 1.59 (d, *J* = 13.2 Hz, 1 H, 2-H), 1.68 (dd, *J* = 2.2, 13.2 Hz, 1 H, 2-H), 1.87, 1.92 (AB part of an ABX system, J_{AB} = 13.0 Hz, J_{BX} = 2.2 Hz, 1 H each, 4-H), 2.62 (m_c, 1 H, 8a-H), 2.67–2.71 (m, 2 H, 6-H), 5.47 (X part, m_c, 1 H, 5-H), 5.85 (m_c, 2 H, 7-H, 8-H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 24.9, 26.2 (2 q, CH_3), 27.0 (t, C-6), 32.2 (s, C-3), 33.9 (q, CH_3), 48.7 (t, C-4), 49.0 (d, C-8a), 55.3 (t, C-2), 74.5 (s, C-1), 120.1 (d, C-5), 124.3, 125.6 (2 d, C-7, C-8), 141.6 (s, C-4a) ppm. Data from mixture: IR (film): ν = 3365 (OH), 2950–2830 (CH), 1630 (C=C) cm^{-1}. HRMS (EI, 80 eV, 60 °C): *m/z* calcd for $C_{13}H_{20}O$ $[M]^+$: 192.1514; found: 192.1513. Anal. Calcd for $C_{13}H_{20}O$ (192.1): C, 81.20; H, 10.48; found: C, 80.93; H, 10.31.
Cyclization of 14
According to the general procedure, the SmI_2 solution in THF (15.8 mL, 1.58 mmol), HMPA (1.66 mL, 9.47 mmol), **14** (0.100 g, 0.53 mmol), and *t*-BuOH (0.078 g, 1.05 mmol) afforded after purification by flash chromatography (hexane–EtOAc, 9:1) compounds **15**, **16**, and **17** as a 74:19:7 mixture in 70% yield (71 mg). Separation by HPLC yielded pure samples.
Analytical Data for (1*S,8a*S**)-1,4,4-Trimethyl-1,2,3,4,8,8a-hexahydronaphthalen-1-ol (15)**
Colorless solid; mp 50–52 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.09, 1.14, 1.17 (3 s, 3 H each, CH_3), 1.35 (dt, *J* = 4.5, 13.6 Hz, 1 H, 3-H), 1.46* (br s, 1 H, OH), 1.47* (ddd, *J* = 2.9, 4.4, 13.6 Hz, 1 H, 3-H), 1.60 (ddd, *J* = 2.9, 4.4, 13.6 Hz, 1 H, 2-H), 1.77 (dt, *J* = 4.5, 13.6 Hz, 1 H, 2-H), 2.47 (tdd, *J* = 3.1, 13.8, 20.0 Hz, 1 H, 8-H), 2.61–2.67 (m, 2 H, 8-H, 8a-H), 5.52 (dddd, *J* = 0.8, 3.3, 5.0, 9.0 Hz, 1 H, 7-H), 5.64 (br d, *J* = 5.7 Hz, 1 H, 5-H), 5.69 (dddd, *J* = 1.4, 3.0, 5.7, 9.0 Hz, 1 H, 6-H) ppm; * overlapping signals. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 20.4 (q, CH_3), 22.7 (t, C-8), 26.2, 28.5 (2 q, CH_3), 35.9 (s, C-4), 38.5, 38.8 (2 t, C-3, C-2), 42.4 (d, C-8a), 75.6 (s, C-1), 115.2 (d, C-5), 122.2 (d, C-6), 123.1 (d, C-7), 145.0 (s, C-4a) ppm. IR (film): ν = 3375 (OH), 2970-2865 (=CH, CH), 1665 (C=C) cm^{-1}.
Analytical Data for (1*S,8a*S**)-1,4,4-Trimethyl-1,2,3,4,6,8a-hexahydronaphthalen-1-ol (16)**
^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.03, 1.08. 1.09 (3 s, 3 H each, CH_3), 1.32 (dt, *J* = 4.2, 13.8 Hz, 1 H, 3-H), 1.43 (ddd, *J* = 2.9, 4.4, 13.8 Hz, 1 H, 3-H), 1.55 (br s, 1 H, OH), 1.63 (ddd, *J* = 2.9, 4.2, 12.9 Hz, 1 H, 2-H), 1.86 (ddd, *J* = 2.9, 4.2, 12.9 Hz, 1 H, 2-H), 2.66–2.70 (m, 2 H, 6-H), 2.97–3.01 (m, 1 H, 8a-H), 5.47–5.51 (m, 1 H, 5-H), 5.81–5.85 (m, 1 H, 7-H), 5.87 (tdd, *J* = 1.8, 3.3, 10.2 Hz, 1 H, 8-H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 21.5, 25.7 (2 q, CH_3), 27.1 (t, C-6), 28.7 (q, CH_3), 34.4 (s, C-4), 37.8, 38.0 (2 t, C-2, C-3), 44.7 (d, C-8a), 71.0 (s, C-1), 116.2 (d, C-5), 124.5, 125.4 (2 d, C-8, C-7), 142.2 (s, C-4a) ppm. IR (film): ν = 3410 (OH), 2960–2810 (=CH, CH), 1650 (C=C) cm^{-1}. HRMS (ESI-TOF-MS): *m/z* calcd for $C_{13}H_{20}ONa$ $[M + Na]^+$: 215.1406; found: 215.1405.

Analytical Data for 1,4,4-Trimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (17)

Colorless solid; mp 68–70 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 1.30, 1.31, 1.55 (3 s, 3 H each, CH_3), 1.68 (br s, 1 H, OH), 1.71–1.83, 1.96–1.99 (2 m, 4 H, 2-H, 3-H), 7.18–7.24 (m, 2 H, Ar), 7.29–7.31 (m, 1 H, Ar), 7.58–7.59 (m, 1 H, Ar) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 30.8, 31.5, 31.7 (3 q, CH_3), 34.06 (s, C-4), 35.9, 36.1 (2 t, CH_2), 71.0 (s, C-1), 126.0, 126.1, 126.4, 127.4 (4 d, Ar), 142.0, 144.7 (2 s, Ar) ppm. IR (film): ν = 3385 (OH), 2960–2860 (=CH, CH), 1660 (C=C) cm^{-1}. HRMS (ESI-TOF-MS): *m/z* calcd for $C_{13}H_{18}ONa$ $[M + Na]^+$: 213.1250; found: 213.1250.

(16) At the moment it is more likely that the isolation of isomeric mixtures is the result of an unselective kinetically controlled protonation. Since equilibration experiments with the products isolated are so far not fully conclusive, further investigation of this problem is required.