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Conversion of a *trans–syn–trans* to a *cis–syn–trans* perhydrobenz[*e*]indenone triggered by intramolecular 1,5-hydrogen transfer

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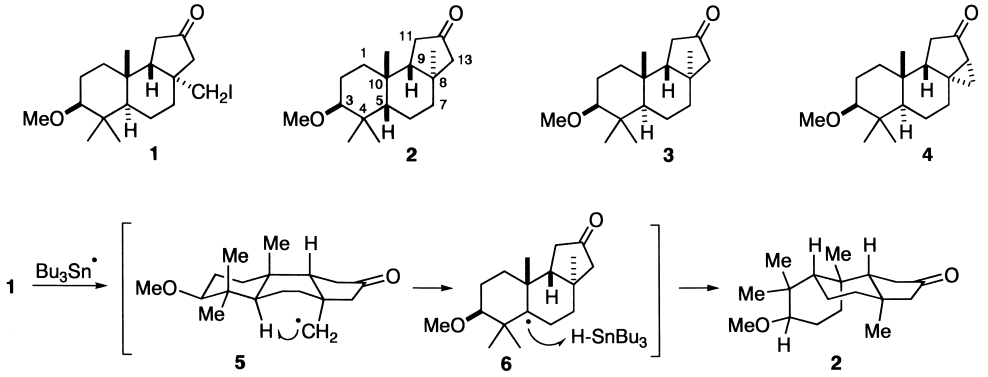
Abstract—The conversion of a *trans–syn–trans* perhydroiodomethyltrimethylbenz[*e*]indenone to the corresponding *cis–syn–trans* perhydrobenz[*e*]indenone occurred during the reduction of the iodomethyl to a methyl group under radical conditions.

In an earlier letter, we have described the synthesis of the tricyclic iodo ketone **1** with *trans–syn–trans* ring junctions and, as a result, a central ring being a twist boat.[1] Its use in the synthesis of cytotoxic marine isomalabaricanes (stellettins,[2] stelliferins,[3] geoditins[4]) required the reduction of the iodomethyl to a methyl group.

Owing to the steric hindrance at the neopentylic iodide, we first attempted its reduction under radical conditions (*n*-Bu_3SnH, AIBN, cyclohexane, reflux, 2 h). We thus obtained only one compound (79% yield) in which H-5 was on the same side as H-9 and Me-10 according to a NOESY experiment. The other NOEs were in agreement with structure **2** having *cis–syn–trans* ring junctions and a central ring in the chair form. Its formation from the radical **5** can be rationalised by (i) transfer of the H-5 hydrogen atom to the proximal methylene radical with formation of a tertiary radical at C-5; (ii) introduction of a hydrogen atom on the β-side of **6** (Scheme 1).

The target ketone **3** could be obtained later by an unoptimised hydrogenolysis of iodide **1** (H_2, 10% Pd/C, NaOAc, MeOH, rt, 1.5 h, 66% yield).[5] Compound **3** was purified by HPLC (semi-preparative Kromasil C_{18} column, methanol/water 65/35) and its structure was established by 2D NMR experiments.



Scheme 1.

Keywords: epimerisation; radicals; reduction; transfer reactions.

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At this stage, we realised that among the two unseparable compounds obtained earlier in the reduction of the cyclopropyl ketone **4** (Li, $EtNH_2$, *t*-BuOH, THF, −78°C, 35 min),[1] the major compound was **3** (61% yield), as already suspected, and the minor compound was **2** with a *cis* A/B ring junction (31% yield). This result can easily be understood since this dissolving metal reduction also proceeds via a methylene radical linked to C-8.

Additional work directed towards the total synthesis of the marine isomalabaricanes is underway in our group.

Spectral data

The NMR assignments are based on COSY, NOESY, DEPT, HSQC, and HMBC experiments.

Ketone **2**: ^{1}H NMR (δ, 500 MHz, $CDCl_3$) 1.03 (s, 3H, Me-8); 1.04 (s, 3H, Me-4α); 1.14 (s, 6H, Me-4β, Me-10); 1.23 (br d, $J=13.0$ Hz, 1H, H-5); 1.29 and 1.32 (2 m, 2H, H-1β and H-7β); 1.48 and 1.53 (dtd, $J=13.2$, 11.8, 3.6 Hz, and m, 2H, H-2β and H-6α)]; 1.72–1.88 [m, 5H; includes signals at 1.75 (dd, $J=14.1$, 7.5 Hz, H-9); 1.78 (td, $J=13.0$, 6.0 Hz, H-1α); 1.82 (H-6β and H-7α); 1.85 (H-2α)]; 2.00 and 2.03 (2 d, $J=16.8$ Hz, 2H, 2 H-13); 2.13 (dd, $J=18.1$, 14.1 Hz, 1H, H-11α); 2.22 (dd, $J=18.1$, 7.5 Hz, 1H, H-11β); 3.02 (dd, $J=11.8$, 4.3 Hz, 1H, H-3); 3.36 (s, 3H, OMe). ^{13}C NMR (δ, 125 MHz, $CDCl_3$) 20.4 (Me-8), 22.6 (C-6), 22.9 (C-2), 26.1 (Me-4β), 26.3 (C-1), 28.9 (Me-4α), 29.7 (Me-10), 36.5 (C-11), 37.0 (C-10), 39.1 (C-7), 39.3 (C-4), 39.4 (C-8), 55.1 (C-5), 55.4 (C-9), 57.7 (MeO), 58.9 (C-13), 84.9 (C-3), 218.1 (C-12). HRMS (m/z) calcd for $C_{18}H_{30}O_2$: 278.2246; found: 278.2252.

Ketone **3**: ^{1}H NMR (δ, 500 MHz, $CDCl_3$) 0.81 (s, 3H, Me-4β); 1.01 (s, 3H, Me-4α); 1.02 (s, 3H, Me-10); 1.15 (d, $J=1.0$ Hz, 3H, Me-8); 1.39–1.69 [m, 6H, includes signals at 1.41 (2 H-1); 1.47 (H-6β); 1.54 (H-2β); 1.64 (br d, $J=13.0$ Hz, H-5); 1.66 (m, H-6α)]; 1.70–1.82 (m, 2H, 2 H-7); 1.89–2.00 [m, 3H; includes signals at 1.92 (dd, $J=13.5$, 8.5 Hz, H-9); 1.94 (d, $J=16.5$ Hz, H-13β); 1.97 (m, H-2α)]; 2.12 (dd, $J=18.0$, 13.5 Hz, 1H, H-11α); 2.15 (d, $J=16.5$ Hz, 1H, H-13α); 2.17 (dd, $J=18.0$, 8.5 Hz, 1H, H-11β); 2.74 (dd, $J=11.5$, 5.0 Hz, 1H, H-3), 3.38 (s, 3H, OMe). ^{13}C NMR (δ, 125 MHz, $CDCl_3$) 16.5 (Me-4β); 17.4 (C-6); 23.0 (Me-10); 23.8 (C-2); 25.7 (Me-8); 29.0 (Me-4α); 33.3 (C-1); 35.3 (C-10); 35.7 (C-11); 36.7 (C-7); 38.7 (C-8); 39.1 (C-4); 47.3 (C-5); 52.6 (C-9); 57.8 (OMe); 60.0 (C-13); 88.8 (C-3); 218.6 (C-12). HRMS (m/z) calcd for $[C_{18}H_{30}NaO_2]^+$: 301.2144; found: 301.2138.

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References

1. Raeppel, F.; Weibel, J.-M.; Heissler, D. *Tetrahedron Lett*. **1999**, *40*, 6377–6381.
2. (a) McCabe, T.; Clardy, J.; Minale, L.; Pizza, C.; Zollo, F.; Riccio, R. *Tetrahedron Lett*. **1982**, *23*, 3307–3310; (b) McCormick, J. L.; McKee, T. C.; Cardellina, J. H., II; Leid, M.; Boyd, M. R. *J. Nat. Prod*. **1996**, *59*, 1047–1050; (c) Tasdemir, D.; Mangalindan, G. C.; Concepcion, G. P.; Verbitski, S. M.; Rabindran, S.; Miranda, M.; Greenstein, M.; Hooper, J. N. A.; Harper, M. K.; Ireland, C. M. *J. Nat. Prod*. **2002**, *65*, 210–214.
3. Tsuda, M.; Ishibashi, M.; Agemi, K.; Sasaki, T.; Kobayashi, J. *Tetrahedron* **1991**, *47*, 2181–2194.
4. Zhang, W.-H.; Che, C.-T. *J. Nat. Prod*. **2001**, *64*, 1489–1492.
5. (a) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary*; John Wiley and Sons: New York, 1978; pp. 121–129; (b) Pinder, A. R. *Synthesis* **1980**, 425–452.