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Syntheses of isomerically pure reference octalins and hydrindanes

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ABSTRACT

We describe herein the development of efficient and stereoselective synthetic routes to a range of *cis*- and *trans*-octalin and hydrindane target compounds.

In the context of a program underway in our laboratory,[1] wherein we are exploring fresh extensions of Diels–Alder-based strategies, we required access to several simple homogeneous, stereochemically defined unsubstituted *cis*- and *trans*-octalins and hydrindanes (compounds **1**–**5**, Fig. 1). Remarkably, a comprehensive survey of the synthetic literature revealed that only a few of the required compounds had been described previously.[2a–e] Moreover, the routes for the synthesis of such compounds gave mixtures of stereoisomers which were not purified. Additional reaction steps would be required to gain access to homogeneous material. For instance, the synthesis of tricyclic *trans*-**3**, accomplished through acid-catalyzed rearrangement of a precursor dodecahydroanthracene, furnished a low yield of the desired compound (15%), along with several other by-products. An analytical sample of *trans*-**3** could be obtained only by preparative gas chromatography. Among the target compounds, only *cis*-**4** was obtained in a stereochemically secure manner, through Diels–Alder reaction of cyclopentadiene with 2,3-dimethyl-1,3-butadiene followed by regioselective hydrogenation of the cyclopentene olefin.

In order to obtain the required quantities of our target systems through viable pathways, we were obliged to devise modified syntheses of the target compounds (**1**–**5**). In this Letter, we relate how these goals were accomplished.

We first describe routes to the *trans*-octalin derivatives, **1**–**3** (Scheme 1). Our key building blocks are the known cyclohexen-1,4-diones, **6a**–**c**, themselves prepared through Diels–Alder reaction of 1,4-benzoquinone with the appropriate dienes (2,3-dimethyl-1,3-butadiene,[2a] isoprene,[2b] and 1,2-dimethylenecyclohexane,[3] respectively). Chemoselective reduction of **6a**–**c** (Zn in aqueous AcOH) yielded the *cis*-diketones **7a**–**c**.[2a,2b] Following literature precedents,[2a] a solution of *cis*-diketone **7a** in 1,4-dioxane was treated with 1 M NaOH (1.07 equiv) at 80 °C for 10 min, to yield the higher melting *trans*-isomer, **8a**. Attempts to achieve epimerization of *cis*-diketones **7b** and **7c** at comparably high temperatures were unsuccessful, leading to low recovery of the desired compounds, and formation of a variety of polar by-products. Epimerization of the *cis*-diketones **7b**–**c** was preferably conducted at room temperature with 1 M NaOH (1.2 equiv) for 10 min to afford **8b** and **8c** in 40% and 79% yields, respectively. However, Wolff–Kishner reduction of

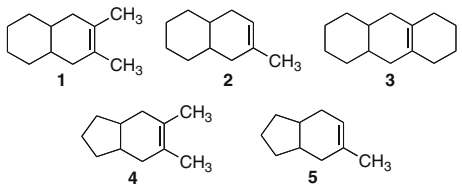
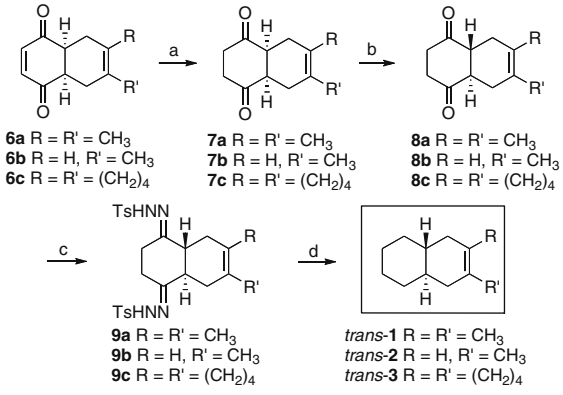


Figure 1. *cis*- and *trans*-decalins and hydrindanes prepared in this study.



Scheme 1. Synthesis of *trans*-**1**, *trans*-**2**, and *trans*-**3**. Reagents and conditions: (a) Zn, AcOH/H_2O (2:1, *v*/*v*), 50 °C or <30 °C, 85% (**7a**), 93% (**7b**), 87% (**7c**); (b) 1.0 M NaOH, 1,4-dioxane, 80 or 23 °C, 10 min, 92% (**8a**), 40% (**8b**), 79% (**8c**); (c) $TsNHNH_2$, EtOH, reflux, 20 min; 72% (**9a**), 85% (**9b**), 78% (**9c**); (d) catecholborane, $CHCl_3$/THF(2:1, *v*/*v*), −10 to 0 °C, 1 h; then $NaOAc{\cdot}3H_2O$, reflux, 1 h, 66% (*trans*-**1**), 82% (*trans*-**2**), 41% (*trans*-**3**).

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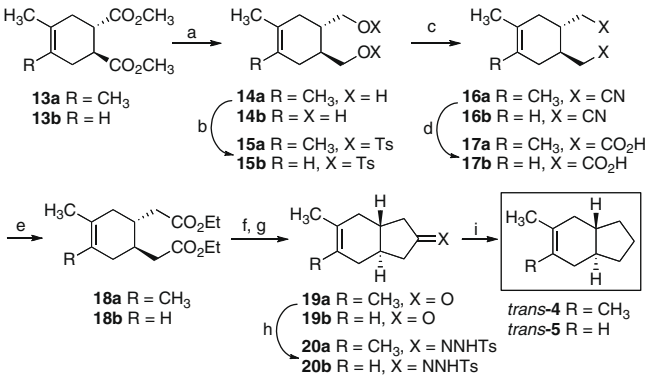
the *trans*-diketones **8a–c** afforded unsatisfactory mixtures of *cis*- and *trans*-olefins **1–3**. Fortunately, reduction[4] of *trans*-bitosylhydrazones **9a–c** (which were readily prepared from **8a–c)** afforded pure octalin derivatives *trans*-**1–3**.

Having synthesized compounds **1–3** in the *trans* series, we next sought to prepare the corresponding *cis*-octalin derivatives, namely *cis*-**1–3** (Scheme 2). The known *cis*-bicyclic ketones, **10a–b**,[5] were prepared by Diels–Alder reaction of cyclohex-2-en-1-one with 2,3-dimethyl-1,3-butadiene and isoprene, respectively, in the presence of catalytic CH_3AlCl_2. The formation of the *trans*-isomeric cycloadducts could be suppressed by conducting the reaction at 0 °C.

Similarly, CH_3AlCl_2-catalyzed Diels–Alder reaction between cyclohex-2-en-1-one and 1,2-dimethylenecyclohexane afforded the tricyclic ketone **10c** in 55% yield. Again, reduction of compounds **10a–c** ($NaBH_4$, CH_3OH, −30 °C) furnished the corresponding carbinols **11a–c** as diastereomeric mixtures of alcohols. All major diastereomers of **11a–c** were separated from their minor isomers by simple column chromatography on silica gel.[6] Actually we could not, at this stage, confidently assign the stereochemistry of the hydroxy-bearing center. In any case, derived Barton–McCombie reduction[7] of xanthate esters **12a–c** gave the target compounds, *cis*-**1–3**.

In accord with Casadevall's observation,[8] the ring junction carbons of *cis*-**1–3** are more shielded than those of *trans*-**1–3**. For example, the ^{13}C NMR chemical shifts of the two ring junction carbons of *cis*-3-methylbicyclo[4.4.0]dec-3-ene (*cis*-**2**) appear at 33.65 and 33.50 ppm as singlets, whereas two singlets are observed at 38.61 and 38.15 ppm in the ^{13}C NMR spectrum of *trans*-**2**.[6]

With the target compounds in the *cis*- and *trans*-octalin series in hand, we next turned our attention to the preparation of the *cis*- and *trans*-hydrindane target compounds, **4** and **5**. Our route to *trans*-**4** and *trans*-**5** began from the known chiral racemic diols, **14a–b**,[9] themselves prepared through Diels–Alder reaction of dimethyl fumarate with the appropriate dienes, followed by $LiAlH_4$ reduction (**13** → **14**). As shown in Scheme 3, diols **14a–b** were converted to ketones **19a–b** using methods analogous to those employed in the preparation of *trans*-bicyclo[4.3.0]non-3-en-8-one.[10] Thus, treatment of **14a–b** with *p*-TsCl in pyridine at 0 °C afforded ditosylates **15a–b**, which were then subjected, without further purification, to the action of ethanolic solutions of sodium cyanide, under reflux. Thus **16a–b** were obtained, which were immediately converted to the corresponding diesters **18a–b** by Fisher esterification. Sequential Dieckmann cyclization, hydrolysis of the resultant β-keto esters, and decarboxylation provided tetrahydroindanones **19a–b**. With the hydrocarbon skeletons of the two *trans*-hydrindane derivatives fully assembled, the remaining task was the deoxygenation of **19a–b**. Treatment of refluxing ethanolic solutions of **19a–b** with *p*-toluenesulfonyl-hydrazide furnished the corresponding tosylhydrazones **20a–b** as white crystalline solids. Reduction of **20a–b** with catecholborane[4] provided the target *trans*-hydrindanes, *trans*-**4** and *trans*-**5**, in 63% and 59% yields, respectively (Scheme 3).

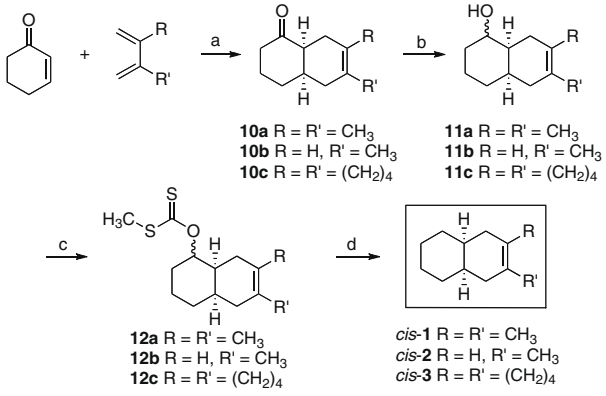


Scheme 3. Synthesis of *trans*-**4** and *trans*-**5**. Reagents and conditions: (a) $LiAlH_4$, THF, 0–23 °C, 60 min, 93% (**14a**), 99% (**14b**); (b) *p*-TsCl, pyridine, 0 °C, 3 h; (c) NaCN, EtOH, reflux, 60 h, 83% over two steps (**16a**), 79% over two steps (**16b**); (d) 6 M KOH, reflux, 24 h; (e) EtOH, H_2SO_4, 48 h, 83% over two steps (**18a**), 81% over two steps (**18b**); (f) NaH, THF, reflux, 2.5 h; (g) DMSO, H_2O, 155 °C, 2.5 h, 81% over two steps (**19a**), 76% over two steps (**19b**); (h) H_2NNHTs, EtOH, reflux, 40 min, 91% (**20a**), 90% (**20b**); (i) catecholborane, $CHCl_3$/THF(2:1, *v*/*v*), −10 to 0 °C, 1 h; then $NaOAc{\cdot}3H_2O$, reflux, 1 h, 63% (*trans*-**4**), 59% (*trans*-**5**).

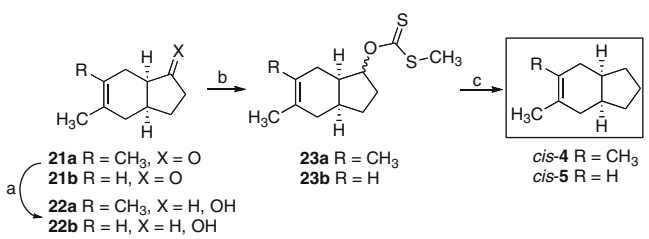
The availability for the first time of these reference compounds enables confident structure assignments in our ongoing Diels–Alder program, the results of which will be described in due course.

Finally, we report the syntheses of the *cis*-fused hydrindanes, *cis*-**4** and *cis*-**5**. As shown in Scheme 4, the known bicyclic ketones **21a–b** were reduced ($NaBH_4$, CH_3OH, −30 °C) to afford alcohols **22a–b** as diastereomeric mixtures, which were then converted to **23a–b** as shown. Treatment of these xanthate esters with nBu$_3$SnH and catalytic amounts of AIBN afforded *cis*-**4** and *cis*-**5**. The ^{13}C NMR spectrum of the former was identical to that reported in the literature.[2e] As observed in the octalin series (vide supra), the ring junction carbons of *cis*-**4–5** are more shielded than those of the corresponding *trans*-isomers. For example, the ^{13}C NMR chemical shifts of the two ring junction carbons of *cis*-3-methylbicyclo[4.3.0]non-3-ene (*cis*-**5**) appear at 36.82 and 35.77 ppm as singlets, whereas two singlets are observed at 42.90 and 42.18 ppm in the ^{13}C NMR spectrum of *trans*-**5**.[6]

In summary, we have described herein the development of workable protocols for the preparation of the *cis*- and *trans*-junction isomers of a range of octalin and hydrindane structures.



Scheme 2. Synthesis of *cis*-**1**, *cis*-**2**, and *cis*-**3**. Reagents and conditions: (a) CH_3AlCl_2 (20 or 50 mol %), CH_2Cl_2, 0 °C, 20–22 h; 70% (**10a**), 53% (**10b**), 55% (**10c**); (b) $NaBH_4$, CH_3OH, −30 to 0 °C, 82% (**11a**), 72% (**11b**), 78% (**11c**); (c) NaH, THF, 23 °C, 30 min; CS_2, 23 °C, 40 min; then CH_3I, 50 °C, 2 h, 98% (**12a**), 99% (**12b**), 93% (**12c**); (d) nBu$_3$SnH, AIBN, benzene, 85 °C, 23% (*cis*-**1**), 17% (*cis*-**2**), 39% (*cis*-**3**).



Scheme 4. Synthesis of *cis*-**4** and *cis*-**5**. Reagents and conditions: (a) $NaBH_4$, CH_3OH, −30 to 0 °C, 96% (**22a**), 95% (**22b**); (b) NaH, THF, 23 °C, 30 min; CS_2, 23 °C, 40 min; then CH_3I, 50 °C, 2 h, 90% (**23a**), 88% (**23b**); (c) nBu$_3$SnH, AIBN, benzene, 85 °C, 40 min, 31% (*cis*-**4**), 15% (*cis*-**5**).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.068.

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