

# Photocyclization–fragmentation route to di- and triquinanes: Stereocontrolled asymmetric synthesis of (–)-isocomene

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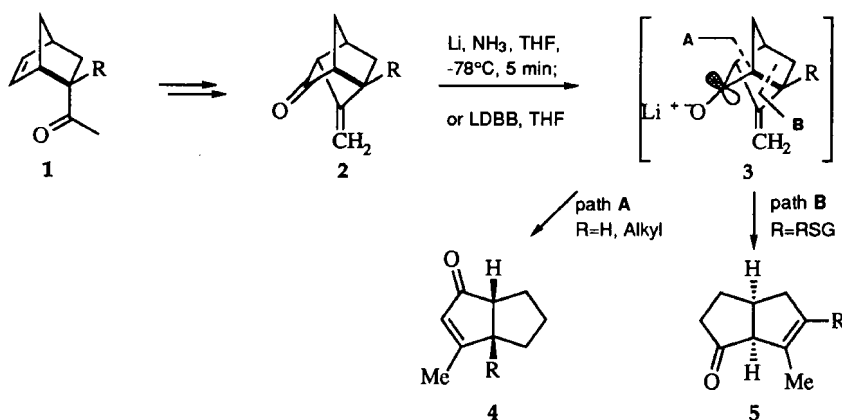
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**Abstract:** We recently reported a general approach to the di- and triquinane frameworks. The strategy takes advantage of two powerful reactions to build the molecular complexity, a Diels-Alder reaction to construct a norbornane, and a Paterno-Büchi reaction to form a latent diquinane. The key step in the strategy is a reductive fragmentation reaction which liberates the quinane skeleton.

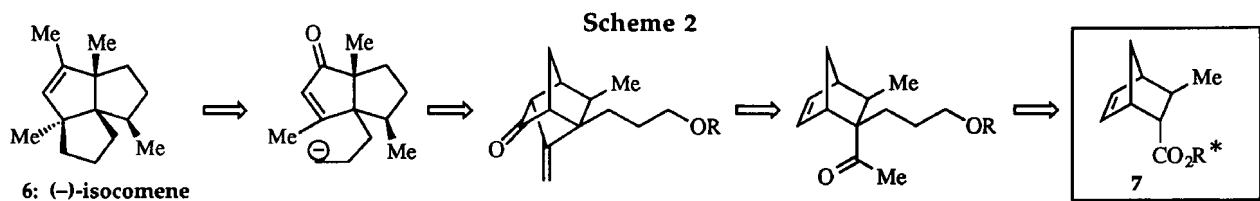
This presentation will focus on the successful implementation of this strategy to the first controlled asymmetric synthesis of (–)-isocomene. The chirality of the natural product is derived from a highly scalemic norbornene ester that is readily available via the Helmchen Diels-Alder reaction. Subsequent elaboration provides a strained ketoalkene. Selective fragmentation of strategic bonds and further transformations afford the natural product in optically pure form, in good overall yield. Recent results aimed at altering the “normal” course of the reductive fragmentation will also be described.

The interesting structural features and the challenge posed by triquinane natural products has stimulated considerable interest in their synthesis. We recently reported a new, general approach to the di- and triquinane frameworks that is well suited for the synthesis of some of these natural products.<sup>1</sup> Our strategy takes advantage of two powerful reactions to build molecular complexity—a Diels-Alder reaction to construct a norbornane, and a Paterno-Büchi reaction to form a latent diquinane (Scheme 1). The resulting highly-strained structures (e.g., **2**) are fragmented with complete selectivity under reductive conditions to reveal quinane skeletons. The fragmentation can follow two different paths, depending on the electronic properties of the substituent (R) on **2**. With alkyl substituted systems, the fragmentation follows only path A and yields diquinane-enones. On the other hand, the alternate fragmentation path takes place when R is a radical stabilizing group (RSG), such as an ester or a phenyl.<sup>2</sup>

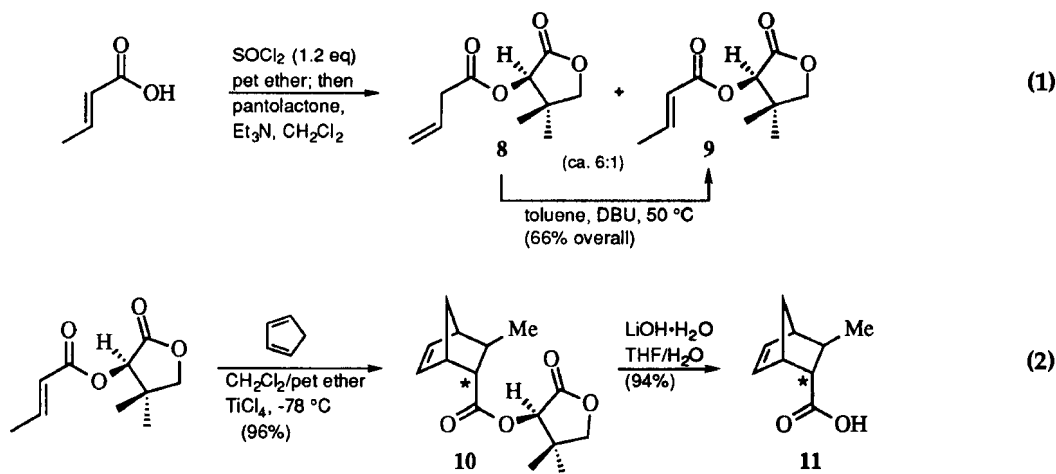
Scheme 1



The power of the overall strategy was successfully demonstrated through a stereocontrolled, *racemic* synthesis of the angular triquinane isocomene.<sup>3</sup> The synthetic route is shown in a retrosynthetic sense in Scheme 2. An important advantage of our route was that it was ideally suited for an asymmetric synthesis of the natural product, the absolute stereochemistry of which had not been established at the time we began this project.<sup>4-6</sup> The starting material for the synthesis was the Diels-Alder adduct of cyclopentadiene and crotonate ester. We expected to be able to make this material in optically pure form by taking advantage of an auxiliary controlled Diels-Alder reaction.



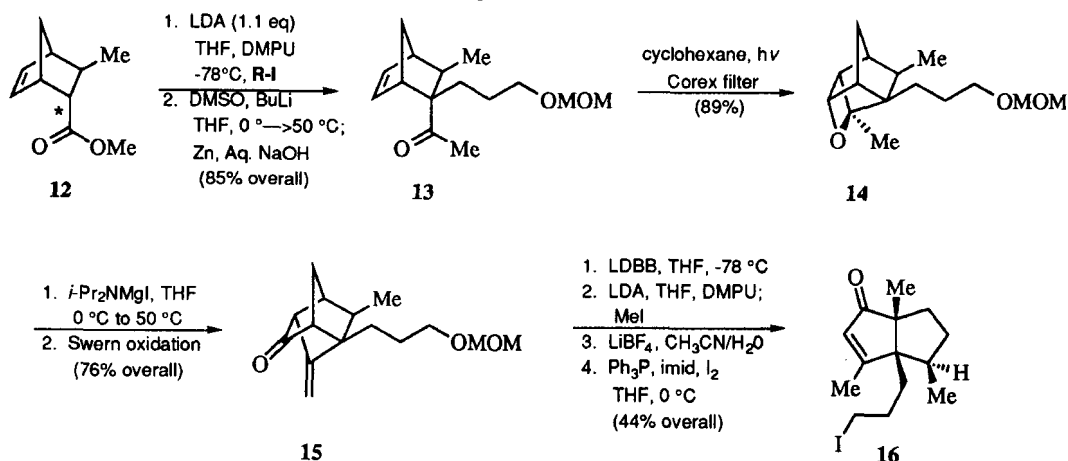
The pantolactone auxiliary, developed by Helmchen, *et al.*, was used for the asymmetric Diels-Alder reaction.<sup>7</sup> The condensation of crotonyl chloride with pantolactone in the presence of triethyl amine yielded the  $\beta,\gamma$ -unsaturated ester **8** as the major product, rather than the expected  $\alpha,\beta$ -unsaturated ester (Eq. 1). The former was readily converted to the latter upon stirring in the presence of a catalytic amount of DBU (10 mol%). The critical asymmetric Diels-Alder reaction was carried out under Helmchen's conditions, using 7:1  $\text{CH}_2\text{Cl}_2$ :petroleum ether with 20 mol%  $\text{TiCl}_4$ , which afforded the cycloadduct in 96% yield after flash chromatography. Analysis of the uncrystallized product by GC showed it to be composed of 93:7 mixture of two predominant diastereomers (Eq. 2). Two recrystallizations from hexane afforded the major diastereomer in >98% purity as colorless crystals, mp 75.5 °C,  $[\alpha]_{\text{D}}^{25} = -113.8^\circ$  ( $c = 3.5$ ,  $\text{CHCl}_3$ ). Removal of the auxiliary using  $\text{LiOH}$  in aqueous THF provided an optically active carboxylic acid,  $[\alpha]_{\text{D}}^{25} = -158.3^\circ$  ( $c = 3.5$ ,  $\text{CHCl}_3$ ), confirming the induction of asymmetry.<sup>8</sup>



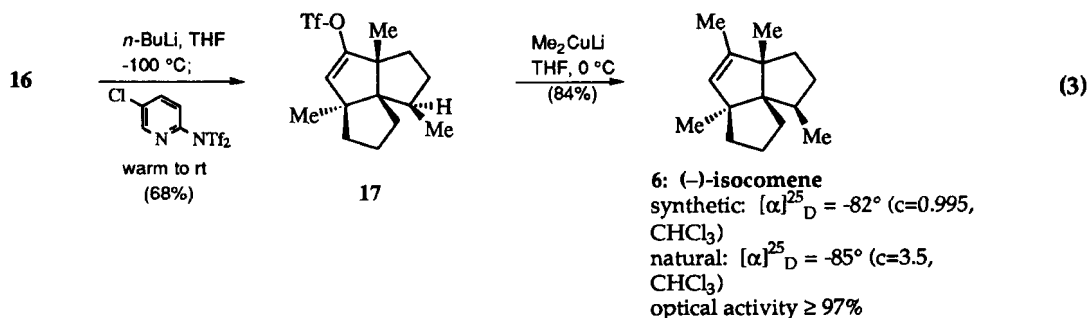
The norbornane carboxylic acid chirality was translated into diquinane chirality via our photocycloaddition-fragmentation strategy as shown in Scheme 3.<sup>1,3</sup> Carboxylic acid **11** proved surprisingly recalcitrant to alkylation<sup>9</sup> by the methoxymethyl (MOM) protected 3-iodopropanol (0-45% yield). This problem was easily solved by conversion of the acid to the methyl ester ( $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ , 94%), the alkylation of which gave in 98% yield the desired product. Exo alkylation was favored 30:1 over endo alkylation. Subjection of ester **12** to Corey's ketone synthesis, followed by a reductive work-

up, gave methyl ketone **13** (87%), which upon irradiation through a Corex filter afforded the Paterno–Büchi product, oxetane **14** in 89% yield.<sup>10</sup> Cleavage of the strained oxetane ring was accomplished under basic conditions to yield a homoallylic alcohol, which was oxidized using the Swern protocol to ketoalkene **15** (76% yield for the two steps). The transfer of the norbornane chirality to the diquinane is achieved in the key reductive fragmentation, effected using lithium di-*t*-butylbiphenylide (LDBB) as the one electron reducing agent. The resulting diquinane, obtained in 63% yield,  $[\alpha]_D^{25} = -16.8^\circ$  ( $c = 1.28$ ,  $\text{CHCl}_3$ ), was deprotonated under kinetic conditions and the enolate was methylated in the presence of DMPU. The MOM protecting group was removed using  $\text{LiBF}_4$  in refluxing aqueous acetonitrile. On treatment with  $\text{PPh}_3$ ,  $\text{I}_2$ , and imidazole in THF, the alcohol was converted into iodide **16** (84%,  $[\alpha]_D^{25} = -14.8^\circ$  ( $c = 1.24$ ,  $\text{CHCl}_3$ )), which was set up for the final ring closure for the angular triquinane skeleton.

Scheme 3



We relied again on the Cooke protocol for the metal halogen exchange–cyclization.<sup>11</sup> Treatment of iodide **16** with 1.1 equivalents of *n*-BuLi allows what would normally be a reversible Lithium–Iodine exchange (Eq. 3). In the present case, however, the anion formed from the exchange can undergo a facile conjugate addition to produce the less basic enolate, thus driving the equilibrium. The cyclization was found to be remarkably fast, going to completion after just 10 min at  $-100^\circ\text{C}$ . Quenching the reaction mixture with Comins' pyridine-derived triflating agent afforded the desired enol triflate in 68% yield,  $[\alpha]_D^{25} = -39.2^\circ$  ( $c = 1.13$ ,  $\text{CHCl}_3$ ).<sup>12</sup> The synthesis was completed by reacting the enol triflate with a large excess of  $\text{Me}_2\text{CuLi}$  (10 equiv), which yielded (–)-isocomene in 84% yield.<sup>13</sup> The rotation of our synthetic material was identical in sign and magnitude (within experimental error) with the natural product, confirming the absolute stereochemistry to be as shown.<sup>14</sup>



Overall, the present synthesis extends the scope and usefulness of our photocycloaddition–reductive fragmentation strategy, to now include the synthesis of enantiomerically pure triquinane natural products.

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