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Asymmetric Synthesis

Expedient and Diastereodivergent Assembly of Terpenoid Decalin Subunits having Quaternary Stereocenters through Organocatalytic Robinson Annulation of Nazarov Reagent

Barbara Berkes,[a] Kristóf Ozsváth,[a] Laura Molnár,[a] Tamás Gáti,[b] Tamás Holczbauer,[a] György Kardos,[a] and Tibor Soós*[a]

Dedicated to the memory of Professor Csaba Szántay

Abstract: We report an expedient approach to highly functionalized *cis*- and *trans*-decalines that could function as key structural subunits toward the synthesis of various classes of terpenoids. Key to the strategy is an organocatalyzed Robinson annulation reaction of the Nazarov reagent that affords chiral enone building blocks with high enantioselectivities. The quaternary carbon stereogenic center can direct the subsequent reactions and allow the rapid and diastereoconvergent assembly of complex decalines with contiguous stereocenters.

Introduction

Despite their evident potential, terpenoids play only a minor role in contemporary pharmaceutical developments because of their structural complexity, limited chemical tractability and availability.[1] Their complex molecular architectures often discourage medicinal chemists to select terpenoids or their structural units as an attractive starting point for drug discovery programs. As a result, one of the focuses of current organic synthesis is the development of streamlined synthetic pathways that can render chemical synthesis as an enabling tool for exploring and leveraging the pharmaceutical potential of terpenoids or their fragments.[2–4] Along these lines, we report a highly expedient, enantio- and diastereoselective synthesis of decalines bearing quaternary stereogenic centers, which are key substructural motifs found in many terpenoids. This accomplishment also serves as a proof-of-principle for the enabling use of cyclohexenones **1** for diastereodivergent synthetic processes.

De novo synthesis of terpenoids is a well-established discipline; however, apart from a few skeletal arrangements, their synthesis remains a highly complex and challenging undertaking.[5] The prominent element of these challenges is the stereoselective construction of quaternary carbon stereocenters,[6] of which terpenoids are richly endowed. These very features of terpenoids resulted in the frequent application of three key building blocks, the Hagemann's ester,[7] the Wieland–Miescher ketone[8] and the Hajos–Parrish ketone,[9] which have clear stereochemical and operational advantages in quaternary carbon stereocenter construction. These venerable compounds have enabled the synthesis of many target compounds of previously perceived impractical complexity. Consequently, further expansion of the repository of easily available intermediates, having even more elaborate structure, is of the utmost importance to underpin streamlined synthetic ventures in terpenoids' chemistry and also in drug development.

We were intrigued to develop methods using easily accessible building blocks that might confer synthetic practicality in total synthesis of several terpenoids. Accordingly, we sought to identify synthetically exploitable structural subunits with quaternary carbon stereocenters in a broad variety of sesqui- and diterpenoids, including drimanes, labdanes, clerodanes, and kauranes. After deliberating over the list of biologically relevant targets, highly oxygenated *cis*- or *trans*-decalines **I** and **II** with contiguous stereocenters and suitable level of functionalities were selected (Figure 1).[10] Accordingly, the goal that served to focus and unify our synthetic efforts was to achieve a highly expedient and stereoselective synthesis of these chiral building blocks.

The above appeal had to be translated into expedient synthetic pathways; therefore, it was envisaged that decaline **I** and **II** structures could be assembled in a concise and divergent manner starting from cyclohexenones **1**. Considering that these chiral starting materials should have enhanced (e.g., double activated olefinic bond) and versatile reactivities and that the quaternary carbon stereocenter might govern the outcome of the subsequent transformations, we reasoned that its Diels–Alder and *iso*-Diels–Alder[11] reactions could be used to form **I** and **II** in a few steps. These skeleton-forming reactions

[a] B. Berkes, K. Ozsváth, L. Molnár, T. Holczbauer, G. Kardos, T. Soós
Institute of Organic Chemistry, Hungarian Academy of Sciences
1519 Budapest, P.O. Box 286 (Hungary)
E-mail: soos.tibor@ttk.mta.hu

[b] T. Gáti
Servier Research Institute of Medicinal Chemistry
Záhony Street 7, 1031 Budapest (Hungary)

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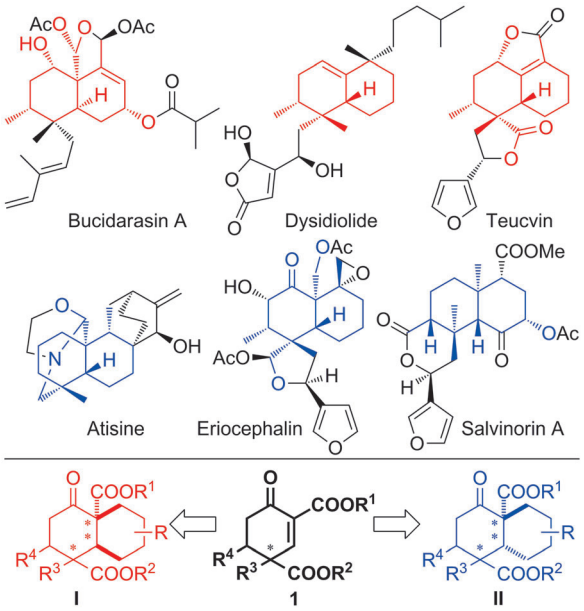


Figure 1. Selected examples of terpenoids having a decaline core and envisioned building blocks.

were devised to be able to simultaneously set up the functionality needed for a broad range of terpenoid targets, including also the requisite array of stereochemistry.

Results and Discussion

Whereas several of these synthetic transformations involved chemistry previously reported in connection with related undertakings,[11,12] the envisioned cyclohexenone **1** has not been forthcoming. Accordingly, as a first foray, we initiated the development of a mild, high yielding and scalable process that could deliver chiral cyclohexenone building blocks **1** with a quaternary carbon stereocenter. As outlined in Figure 2, we envisioned that our goal could be achieve in an organocatalytic Robinson-type annulation between Nazarov reagent **2** and prochiral 2-formylester **3**. Despite this apparently simple and direct approach, several synthetic challenges lay ahead. Although there have been ample precedents for the organocatalytic application of Nazarov reagent **2**,[13] none of those reactions were Robinson-type annulations.[14] In those transformations, the bifunctional Nazarov reagent **2** functioned as a nucleophilic reagent because it sequentially acted as a Michael donor and then a Michael acceptor. An additional technical problem is that the Nazarov reagent **2** has a restricted use in some annulations because of its instability.[15] Nevertheless, with the insight gained from bifunctional organocatalysis,[16,17] we questioned whether it would still be possible to reverse the order of reactivity by employing a more C–H acidic nucleophile as a substrate.

We chose the annulation of the Nazarov reagent **2a** with 2-methyl-3-oxopropanoate **3a** shown in Table 1 as a model reaction to identify an efficient organocatalyst and appropriate reaction conditions. First, the viability of the annulation strategy was confirmed because the reaction afforded the desired product (**1a**) when triethylamine was applied as a catalyst (Table 1, entry 1). We then undertook a systematic investigation of bifunctional thiourea and squaramide organocatalysts, because of their commanding performance in asymmetric Michael addition reactions. The quinine-based thiourea catalyst **4a**[17a,18] and the analogous Takemoto's catalyst[19] **4b** showed moderate performance, furnishing product **1a** with modest yields and enantioselectivities (entries 2 and 3). However, variation of the thiourea moiety of the catalyst with more acidic double hydrogen-bond donor squaramide[20] revealed that it had a large influence on the enantioselectivity, with catalysts **5a–c** affording significantly improved enantioselectivities (entries 4–6). This gave us impetus to uncover structural features of bifunctional squaramide organocatalysts that could significantly affect the enantiomeric excess of the model reaction.

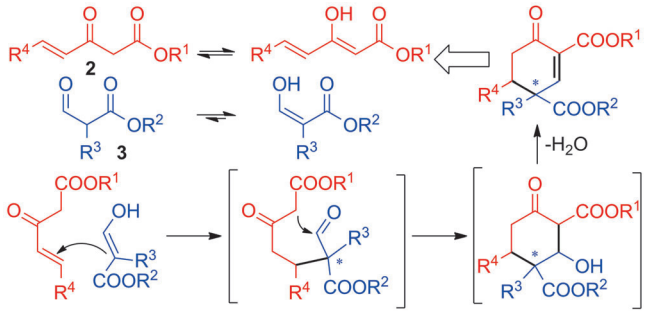
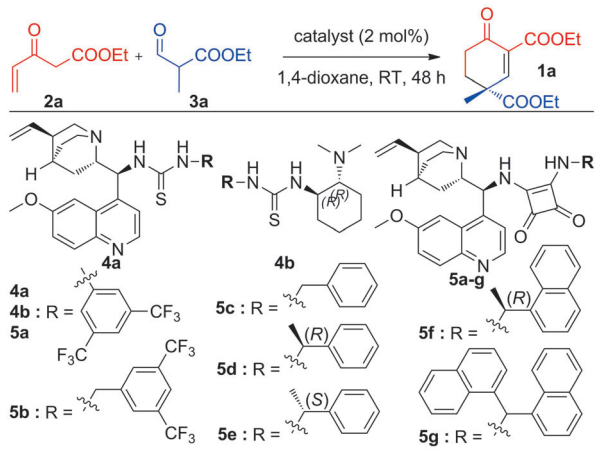


Figure 2. Tautomerization of bifunctional reagents **2** and **3** and their envisaged cascade reaction to afford **1**.

We were intrigued by the observation that introduction of an additional chiral element adjacent to the squaramide moiety in catalyst **5d** led to a higher *ee* value (Table 1, entry 6 vs. 7); however, use of the diastereomeric catalyst **5e** (entry 7 vs. 8) resulted in only a slight improvement. Accordingly, the configuration of the benzylic position played a negligible role in the performance of these catalysts. Therefore, we presumed that the steric hindrance might be more important for the catalyst's efficiency enhancement. Thus, sterically more crowded systems were probed by utilizing naphthalenyl and binaphthalenyl derivatives **5f** and **5g**. These structural tunings led to notable improvements, with the sterically most crowded catalyst **5g** displaying a superior efficiency in the model reaction (entry 10). At this stage, we also noted that running the reaction at ambient temperature and the use of 1,4-dioxane as solvent was essential for realization of the desired enantioinduction.[21]

Having established effective conditions for the model reaction, the scope of this organocatalytic Robinson annulation reaction was then explored. As revealed in Table 2, the reaction was amenable to changes in steric features of the reacting partners. Nazarov reagents **2a–c**, bearing different alkyl substituents on the ester group, underwent clean reactions, affording the desired cyclized products **1a–c**. Moving from methyl (**2b**) to *tert*-butyl (**2c**) esters resulted in slightly higher yields and enhanced levels of enantioenrichment. Subsequently, the scope of the reaction with respect to the 2-methyl-3-ox-

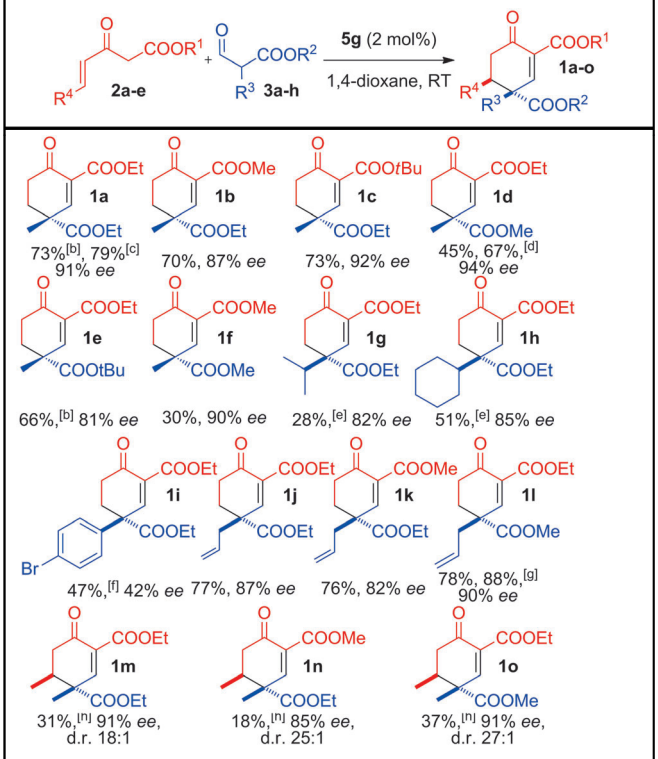
Table 1. Robinson annulation of Nazarov reagent (**2a**) with prochiral 2-formyl ester **3a** promoted by bifunctional organocatalysts.[a]



Entry	Catalyst	Conv. [%][b]	*ee* [%][c]
1[d]	TEA	74 (71)	–
2	**4a**	47	61
3	**4b**	65	−66[e]
4	**5a**	72	79
5	**5b**	62	77
6	**5c**	73	83
7	**5d**	71 (68)	85
8	**5e**	68	86
9	**5f**	64	89
10	**5g**	78 (73)	91

[a] Unless otherwise specified, all reactions were conducted with the Nazarov reagent (**2a**; 0.4 mmol), ethyl 2-methyl-3-oxopropanoate (**3a**; 1.1 equiv, 0.44 mmol) and catalyst (0.008 mmol, 2 mol%) in 1,4-dioxane (0.4 mL) at room temperature for 48 h. [b] Conversion was determined by GC-MS spectroscopic analysis of the crude mixture with hexadecane as internal standard; the data in parentheses are the yields of isolated products after column chromatography. [c] Determined by HPLC analysis using a chiral stationary phase (Daicel Chiralpak IC column). [d] 20 mol% TEA was used as a catalyst. [e] Opposite enantiomer. TEA = triethylamine.

Table 2. Scope of the organocatalytic Robinson annulation of Nazarov reagent.[a]



[a] Unless otherwise noted, the reactions were performed with **2a–e** (3 mmol), **3a–h** (3.3 mmol), and catalyst **5g** (0.06 mmol) in 1,4-dioxane (3 mL) at 25 °C for 3 days. The yields of isolated products were determined after column chromatography on silica gel. The *ee* and the d.r. were determined by HPLC analysis on a chiral stationary phase. [b] Reaction time was 2 days. [c] The reaction was carried out on a 6 mmol scale for 2 days. [d] The reaction was carried out on a 60 mmol scale for 4 days. [e] Reaction time was 4 days. [f] Reaction time was 7 days. [g] The reaction was carried out on a 30 mmol scale for 4 days. [h] 0.12 mmol of catalyst **5g** in 1,4-dioxane (1.5 mL) and THF (1.5 mL) was stirred for 7 days.

opropanoate was investigated. This survey revealed an exactly opposite trend across the surveyed small, medium, and large ester variants; the sterically more bulky *tert*-butyl ester (**3c**) substantially retarded the stereoselectivity of the process (**1e** vs. **1a**, **1d** and **1f**). Next, variation of the α-substituents of the prochiral 3-oxopropanoate was studied. By using linear or branched alkyl substituents, such as isopropyl (**3d**), cyclohexyl (**3e**) or allyl (**3g**, **3h**), the reaction performed well. Efforts to extend the scope of the reaction with respect to the nucleophilic partner toward α-aryl substituted derivatives (**3f**) were also probed; however, both the yield of **1i** and the enantioselectivity significantly decreased.

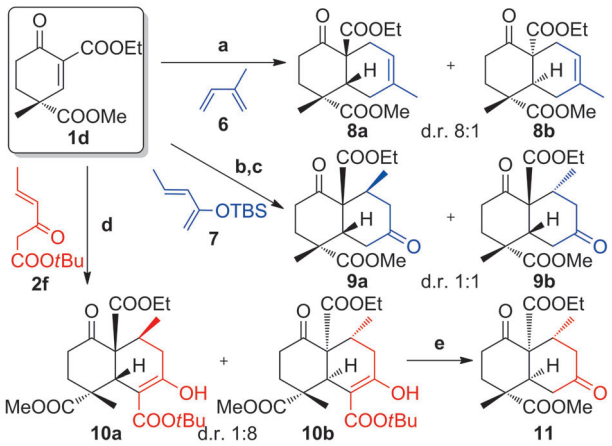
The formation of the cyclohexenone products **1a–i** has been limited to the use of the unsubstituted Nazarov reagents **2a–c**. Nevertheless, we wondered whether β-substituted Nazarov reagents could be suitable partners in this organocascade reaction. Since the β-alkyl substituent should deactivate the Nazarov reagent for both electronic and steric reasons, the outcome of this reaction was questionable. Pleasingly, when **3a**,**b** was reacted with methyl substituted Nazarov reagent **2d**,**e** in the presence of 4 mol% catalyst **5g**, the desired cyclohexenones **1m–o** were obtained with high enantio- and diastereoselectivity, albeit in low yield.[22]

To showcase the scalability and practicality of this Robinson annulation methodology, we performed reactions with selected substrates on a larger scale (30–60 mmol). Pleasingly, the desired enones **1a**, **1d**, and **1l**, bearing the quaternary carbon stereocenter, were obtained with high conversions without altering enantioselectivities (Table 2).

Having established the methodology to construct cyclohexenones with an allylic stereogenic quaternary carbon, we wished to demonstrate their potential and versatility for the targeted synthesis of bicyclic structures **I** and **II**. Along these lines, we examined a range of Diels–Alder and *iso*-Diels–Alder strategies to reach possible diastereomers of the envisioned *cis*- and *trans*-fused decaline fragment.

Initially, we explored the feasibility of using the Diels–Alder route to transform cyclohexenone **1d** into *cis*-decalines bearing an additional quaternary stereogenic carbon center at the ring junction (Scheme 1). Under achiral Lewis acid promotion, isoprene (**6**) and silyloxy-butadiene **7** underwent ready reac-

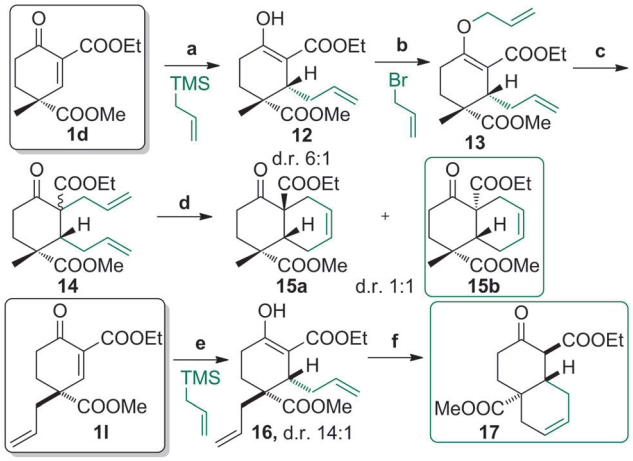
tions to afford *cis*-decalines **8a** and **9a**,**b** products with complete regioselectivity and, most importantly, high π-facial diastreoselectivity. Accordingly, the incorporation of a quaternary stereogenic center in the allylic position of dienophile **1d** exerted directing influence in a non-chelation pathway. Given that the preferred approach of the investigated dienes was *syn* to the more bulky ester group, it seems that the electronic control could override the steric effect in this reaction.[23] It is also revealed that there was no *exo*/*endo* selectivity when silyloxy-butadiene **7** reacted; however, these diastereomers could be separated by chromatography.



Scheme 1. Diastereodivergent construction of *cis*-decalines. Reagents and conditions: a) $ZnCl_2$ (2 equiv), Et_2O, 0–25 °C, 71% yield; b) $ZnCl_2$ (2 equiv), Et_2O, 0–25 °C; c) TFA, CH_2Cl_2, 25 °C, 88% yield over two steps; d) Cs_2CO_3 (1.5 equiv), EtOAc, 25 °C, 68% yield; e) *p*TsOH, toluene, 80 °C, 88%; *p*TsOH = *p*-Toluenesulfonic acid.

An "anionic Diels–Alder reaction", the Deslongchamps annulation[24] was then probed. As an emerging methodology for the synthesis of *cis*-decalines, the method fuses the cesium enolate of the Nazarov reagents with highly reactive cyclohexenone-type dienophiles. Pleasingly, the Nazarov reagent **2f** underwent Cs_2CO_3-promoted annulation with cyclohexenone **1d** to generate *cis*-decalines **10a**,**b** with reversed π-facial diastereoselectivity. This type of annulation thus establishes a preference for *trans* addition with the carboxylic substituents of **1d** in competition with a methyl group. The reversal of facial diastereoselectivity encountered is unexpected, but hold significant synthetic promise: the Diels–Alder and the Deslongchamps annulation seem to be complementary approaches for the controlled construction of contiguous stereocenters in the targeted *cis*-decalines. As exemplified, three out of the four possible stereoisomers of *cis*-decalines were prepared in a concise manner (**9a**, **9b**, and **11** in Scheme 1).

Having thus developed diastereodivergent methodologies from **1d** for the synthesis of *cis*-decalines, we then sought to establish concise routes to *trans*-decalines **II** from the same chiral precursor. To this end, we considered applying the *iso*-Diels–Alder sequence developed by Danishefsky.[11] As outlined in Scheme 2, this route was realized in a four-step sequence. The requisite metathesis precursor was constructed through Hosomi–Sakurai allylation[25] followed by alkylation of the resultant **12** enol with allyl bromide. Pleasingly, the Hosomi–Sakurai reaction proceeded with high diastereoselectivity, and the same sense of diastereoselectivity was observed as in Diels–Alder reactions. Attempts to directly C-alkylate enol **12** failed, which might be a consequence of 1,3-axial interaction with the existing stereogenic quaternary center. However, a stepwise O-allylation reaction followed by a thermal Claisen rearrangement afforded the desired **14** diallyl compound, albeit as an inseparable 1:1 stereoisomer. The subsequent ring-closing metathesis proceeded in high yields and afforded chromatographically separable **15a**,**b** *cis*- and *trans*-decalines.



Scheme 2. Synthetic routes toward *trans*-decalines. Reagents and conditions: a) allyl trimethylsilane, $ZnCl_2$ (1 equiv), CH_2Cl_2, 0–25 °C, 87% yield; b) allyl bromide, Cs_2CO_3, DMF, 0–25 °C, 82%; c) neat, 150 °C, 24 h; d) Hoveyda–Grubbs Catalyst 2nd generation (5 mol%), CH_2Cl_2, 25 °C, 93% over two steps; e) allyl trimethylsilane, $ZnCl_2$ (1 equiv), CH_2Cl_2, 0–25 °C, 91% yield; f) Hoveyda–Grubbs Catalyst 2nd generation (5 mol%), CH_2Cl_2, 25 °C, 72% yield.

Being cognizant of the diastereoselectivity of the Hosomi–Sakurai reaction of **1d**, we presumed that allyl substituted cyclohexanone **1l** would also be amenable to the construction of *trans*-decaline. Thus, chiral enone **1l** was subjected to Hosomi–Sakurai allylation by using achiral $ZnCl_2$ catalyst. Again, high diastereoselectivity was observed in this allylation reaction (d.r. 14:1). The resultant diallyl compound **16** easily underwent ring-closing olefin metathesis to deliver the desired *trans*-decaline **17** in high yield.

Conclusions

An organocatalytic Robinson-type annulation of Nazarov reagent was realized that afforded cyclohexenones bearing a quaternary carbon stereocenter. These chiral products have several useful features: 1) their synthesis is enantioselective, diastereoselective, and scalable, and 2) the stereogenic quaternary center of the scaffold allows exquisite diastereochemical control in the course of subsequent synthetic elaborations toward *cis*- and *trans*-decalines in multigram scale with contiguous quaternary and tertiary stereocenters. These rigid, poly-

functional three-dimensional scaffolds can facilitate the synthesis of many natural products and can also be expected to be prime starting points for drug discovery programs based on terpenoid-derived fragments. Further studies exploiting these building blocks in the total synthesis of complex terpenoids are under way in our laboratory.

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Keywords: asymmetric synthesis · diastereoselectivity · fused-ring systems · organocatalysis · terpenoids

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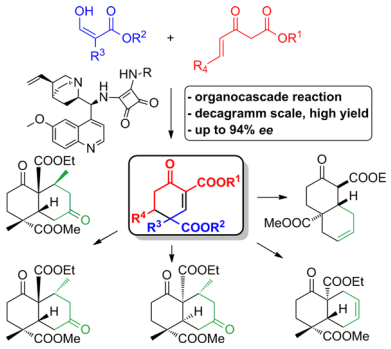
FULL PAPER

Reaching the start: An expedient approach to highly functionalized *cis*- and *trans*-decalines has been developed (see scheme). Key to the strategy is an organocatalyzed Robinson annulation reaction of the Nazarov reagent to afford chiral enone building blocks with high enantioselectivities. The quaternary carbon stereogenic center can direct the subsequent reactions and allow the rapid assembly of complex decalines in a diastereodivergent manner.



Asymmetric Synthesis

*B. Berkes, K. Ozsváth, L. Molnár, T. Gáti, T. Holczbauer, G. Kardos, T. Soós**

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Expedient and Diastereodivergent Assembly of Terpenoid Decalin Subunits having Quaternary Stereocenters through Organocatalytic Robinson Annulation of Nazarov Reagent