Natural Product Synthesis

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A Diels–Alder Approach to (−)-Ovalicin**

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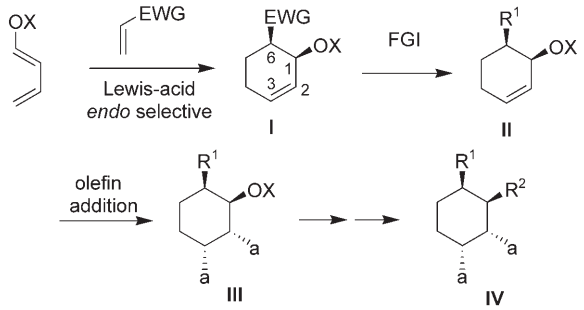
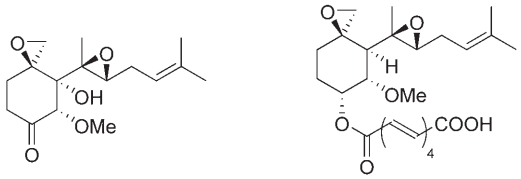
Dedicated to Professor Lutz F. Tietze on the occasion of his 65th birthday

A fascinating aspect of the Diels–Alder reaction is its *endo* selectivity. This *endo* preference is much less pronounced in intermolecular cases compared with the intramolecular and transannular Diels–Alder (IMDA and TADA) reactions.[1] Nevertheless, high *endo* selectivity is observed in the Diels–Alder additions of (*E*)-1-O-substituted dienes catalyzed by Lewis acids that lead to *cis*-1,6-disubstituted cyclohexene systems of type **I** (Scheme 1).[2] Compounds of type **I** could be used as a temporary means to control the stereogenic centers at C2 and C3. For example, the substituent at C1 in **I** and **II** should direct additions to the opposite face of the ring to give **III** selectively. Subsequently, the substitution at C1 may be transformed to give the desired substitution pattern **IV**.



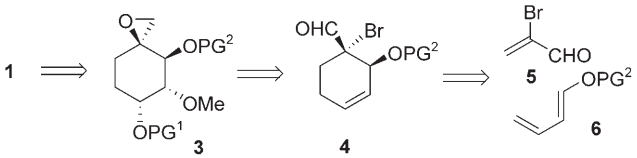
Scheme 1. Strategy to reach highly functionalized cyclohexane derivatives. EWG = electron-withdrawing group, FGI = functional-group interconversion, X = SiR_3, acyl, alkyl.

We chose ovalicin (**1**), a sesquiterpene alkaloid first isolated from cultures of the fungus *Pseudorotium ovalis* Stolk as a target for this strategy.[3] Compound **1** and the structurally closely related fumagillin (**2**) (Scheme 2) have sparked scientific interest because of their potent antiangiogenic activity.[4] In addition, **1** is a promising agent against microsporidiosis.[5]



Scheme 2. Natural products with antiangiogenic activity.

Although a Diels–Alder reaction was employed in two of the reported total syntheses of fumagillin (**2**),[6] it has not been used in the reported syntheses of ovalicin (**1**).[7] From our retrosynthetic plan, **3** and **4** emerged as key intermediates that could originate from the Diels–Alder reaction between **5** and **6** (Scheme 3).



Scheme 3. Retrosynthetic analysis of ovalicin (**1**). PG = protecting group.

Several attempts to develop a catalytic enantioselective Diels–Alder reaction of **5** and various derivatives of **6**, such as 1,3-butadienyl benzoate (**7**), *tert*-butyldimethylsiloxy-1,3-butadiene (**8**), or *para*-methoxybenzyl-oxy-1,3-butadiene (**9**), failed to produce results with reasonable enantioselectivities (Table 1). The best results were obtained from reactions of the titanium-based Keck (**A**) and Mikami (**B**) catalysts[8,9] (Scheme 4) with diene **7** (Table 1, entries 1 and 3; 56 and 45% *ee*, respectively). No selectivity was observed using diene **8** even at −78°C (entry 2). Diene **9** proved to be unstable towards the Keck and Mikami catalysts, even at −78°C. Use of the Corey (*S*)-tryptophan-derived oxazaborolidine[10] (**C**) failed to give selectivities with diene **8** and **9** (entries 4 and 5). Diene **7** did not react in the presence of **C**, and was recovered from the reaction. Also the imidazolidinone catalyst (**D**) reported by MacMillan et al.[11] showed only negligible selectivity with **7** (entry 6). Thus the electron-rich dienes **8** and **9** are too reactive to need catalysis. The electron-poor ("slow") diene **7** does react under catalysis, although without much induction of asymmetry.

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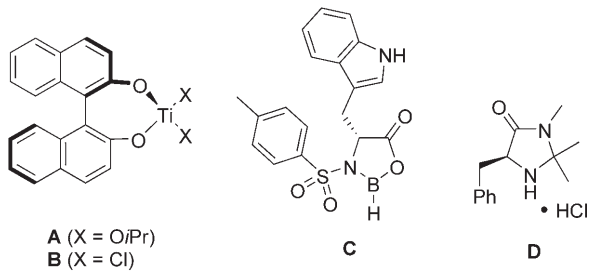
Table 1: Selection of the attempted enantioselective Diels–Alder cycloadditions of **5** with various dienes.

Entry	Catalyst[a]	Diene[b]	*T*, *t*	Yield [%][c]	*ee* [%][d]
1	**A**	OBz **7**	4 °C, 18 h	42	56
2	**A**	OTBS **8**	−78 °C, 1.5 h	73	< 10
3	**B**	OBz **7**	4 °C, 18 h	41	45
4	**C**	OTBS **8**	−78 °C, 6 h	44	< 10
5	**C**	OPMB **9**	−30 °C, 5 h 20 °C, 12 h	58	< 10
6	**D**	OBz **7**	4 °C, 18 h	74	< 10

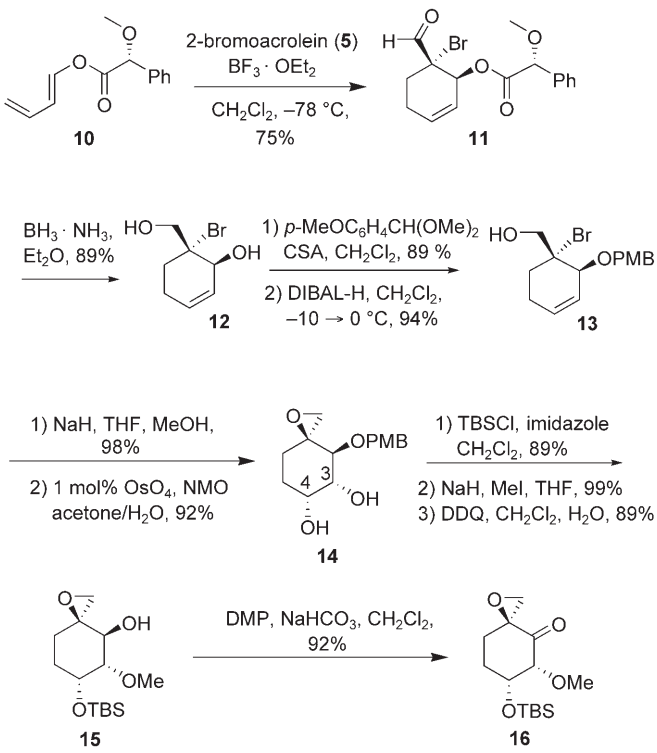
[a] **A** = Keck catalyst;[8] **B** = Mikami catalyst;[9] **C** = Corey catalyst derived from (*S*)-tryptophan;[10] **D** = MacMillan imidazolidinone;[11] [b] Bz = benzoyl, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl; [c] yields of isolated product; [d] determined by HPLC analysis on a chiral stationary phase and by analysis of 250 MHz ^{1}H NMR spectra using the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]



Scheme 4. Chiral catalysts tested for the enantioselective Diels–Alder reaction.

Instead of screening a library of chiral catalysts, we turned to chiral auxiliaries, and very soon found that butadiene **10** reported by Trost et al.[12] gave adduct **11** with good *endo* selectivity (d.r. 8:1) in 75% yield after chromatographic separation (Scheme 5). The stereochemical implications of Diels–Alder additions with the Trost diene have been discussed in detail previously.[13]

As a result of the lability of the ester group in **11** under reductive and nucleophilic conditions, it was necessary to introduce a stable protecting group. Classical saponification conditions (K_2CO_3 in MeOH) led to rapid decomposition of the starting material **11**. Therefore, we decided to convert **11** into diol **12** and to selectively protect the secondary alcohol by using the *para*-methoxybenzylidene acetal formation and reduction procedure.[14] Reduction of **11** with DIBAL-H gave only low yields of **12**. We overcame this problem by using an excess of borane ammonia complex, thus affording diol **12** in 89% yield. At this stage, 90% of the chiral auxiliary was recovered in form of the alcohol and could be recycled in one step by oxidation.[15] Diol **12** was converted into the *para*-



Scheme 5. Synthesis of the core fragment. CSA = (±)-camphor-10-sulfonic acid, DIBAL-H = diisobutylaluminum hydride, NMO = 4-methylmorpholine *N*-oxide, DDQ = 2,3-dicyano-5,6-dichloro-parabenzoquinone, DMP = Dess–Martin periodinane.

methoxybenzylidene acetal and reduced to the PMB-alcohol **13** with DIBAL-H. The epoxide was formed from **13** using an intramolecular S_N2-type substitution in excellent yield. Subsequent dihydroxylation afforded the diol **14** in high diastereoselectivity. The NMR coupling constants indicated that the hydroxy group at C3 in **14** occupies an equatorial position and should therefore be more reactive. Nevertheless, since the hydroxy function at C3 is sterically encumbered by the vicinal OPMB group, we were able to protect selectively the axial hydroxy group at C4 with TBSCl. Use of the less bulky triethylsilyl chloride led mainly to 3,4 disilylation. After methylation and removal of the PMB group, the crystalline alcohol **15** was isolated and characterized by X-ray analysis.[16] Interestingly the bulky TBS group was found to still occupy the axial position. Oxidation with Dess–Martin periodinane produced the core fragment **16**.

We next turned to the synthesis of side chain **17**. Surprisingly, even after numerous repetitions and modifications, the published route[6b] only gave an inseparable (ca. 4:1) mixture of **17** and its isomer **18** (Scheme 6). For this reason, we had to develop an alternative route.

Scheme 6. Products formed following the published route.[6b]

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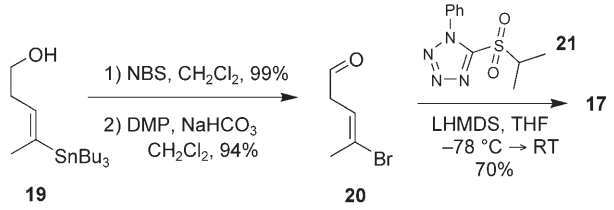
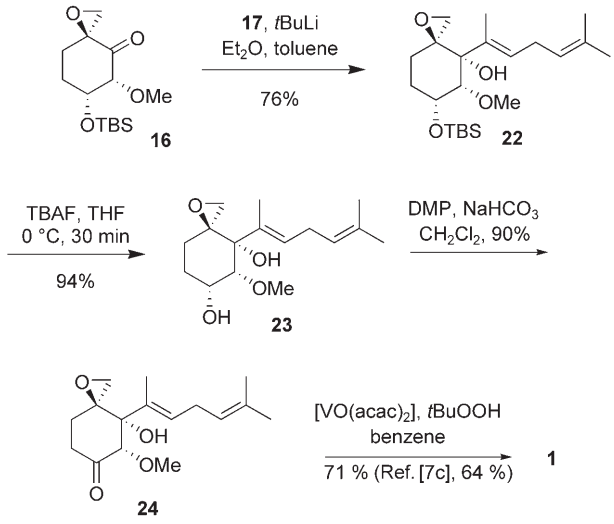
Vinyl stannane **19**,[17] which was prepared in one step from 2,3-dihydrofuran, was brominated with NBS and then oxidized to the labile aldehyde **20** (Scheme 7). Wittig olefination of **20** failed, but the Julia–Kocienski[18] reaction with sulfone **21** furnished the isomerically pure (*E*)-vinylbromide **17** in good overall yield.



Scheme 7. Synthesis of the side chain. NBS = *N*-bromosuccinimide, LHMDS = lithium hexamethyldisilazide.

Freshly prepared vinylbromide **17** was lithiated with *tert*-butyllithium and coupled to the core fragment **16** to yield alcohol **22** stereoselectively (Scheme 8). Removal of the TBS group proceeded smoothly with tetra-*n*-butylammonium



Scheme 8. Completion of total synthesis. TBAF = tetra-*n*-butylammonium fluoride, [VO(acac)$_2$] = vanadyl acetylacetonate.

fluoride at 0 °C to deliver the known diol **23**.[7c] Oxidation with Dess–Martin periodinane and stereoselective epoxidation[7a,c] yielded (−)-ovalicin (**1**), of which the analytical data were fully in accord with those of natural ovalicin. See the Supporting Information.

In summary, ovalicin was prepared in 15 linear steps enantio-, diastereo-, and regioselectively with an overall yield of 15%. The efficiency of the synthesis depended on the excellent *endo* selectivity of the initial Diels–Alder reaction that paved the way for all the equally selective transformations to follow.

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for 10 s over a 1° scan width. The structure was solved by direct methods and refined by full-matrix least-squares techniques. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were placed at calculated positions (except H9 which was localized from difference Fourier syntheses) and refined as riding atoms. Structure solution and refinement was performed with the SHELX program SHELX-74 program (G.M. Sheldrick, *Program for crystal structure solution*, Universität Göttingen, **1997**; G.M. Sheldrick, *Program for crystal structure refinement*, Universität Göttingen, **1997**). CCDC-627132 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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