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Asymmetric [4 + 3] Cyloadditions between Vinylcarbenoids and Dienes: Application to the Total Synthesis of the Natural Product (−)-5-*epi*-Vibsanin E

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Abstract

The total synthesis of (−)-5-*epi*-vibsanin E (**2**) has been achieved in 18 steps. The synthesis combines the rhodium-catalyzed [4 + 3] cycloaddition between a vinylcarbenoid and a diene to rapidly generate the tricyclic core with an effective end game strategy to introduce the remaining side-chains. The [4 + 3] cycloaddition occurs by a cyclopropanation to form a divinylcyclopropane followed by a Cope rearrangement to form a cycloheptadiene. The quaternary stereogenic center generated in the process can be obtained with high asymmetric induction when the reaction is catalyzed by the chiral dirhodium complex, Rh_2(*S*-PTAD)$_4$.

Two striking examples of highly functionalized cycloheptane natural products are (−)-vibsanin E (**1**) and (−)-5-*epi*-vibsanin E (**2**), each containing five stereogenic centers within the cycloheptane ring. Vibsanin E (**1**) was first isolated by Kawazu from the Japanese fish poison plant *Viburnum odoratissimum* (Sangoju) in 1978,[1] whereas 5-*epi*-vibsanin E (**2**) was isolated 24 years later by Fukuyama from *Viburnum awabuki* (Caplifoliaceae).[2] Several synthetic approaches to these targets have been reported,[3] a number of which have resulted in the formation of stereoisomers of **1** and **2**. Their total syntheses, however, has remained elusive. This paper will describe the application of the [4 + 3] cycloaddition between vinylcarbenoids and dienes to the asymmetric synthesis of (−)-5-*epi*-vibsanin E (**2**). The synthetic approach is a collaborative effort exploiting the vinylcarbenoid chemistry developed by the Davies group[4] and the end-game synthetic strategies devised by the Williams group.[5]

The Davies group has developed a general method for the stereoselective construction of seven-membered rings **5** by means of a formal [4 + 3] cycloaddition between vinyldiazoacetates **3** and dienes (Scheme 1).[4] The reaction proceeds *via* a cyclopropanation to form divinylcyclopropanes **4**, which undergo a Cope rearrangement to form **5** with excellent stereocontrol. The reaction occurs with a range of substrates and in selected systems, highly enantioselective reactions are possible. The dirhodium tetraprolinate catalyst Rh_2(*S*-DOSP)$_4$ gives high asymmetric induction in the [4 + 3] cycloaddition providing that R^1 in the vinyldiazoacetate **3** is a methyl ester, R^3 is alkyl or aryl, and R^2 and R^4 are unfunctionalized.

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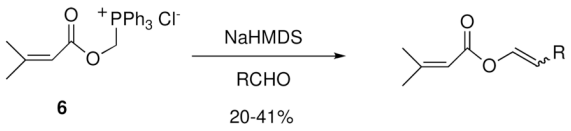
[4b] Recently, Rh_2(*S*-PTAD)$_4$ has been shown to be an effective chiral catalyst for the synthesis of tropanes by a [4 + 3] cycloaddition between 3-siloxy-2-diazobutenoate and *N*-Bocpyrroles,[4c] and hence was predicted to be effective for this system.

One of the most challenging problems in the late stage strategy for the synthesis of seven membered ring vibsanins is the synthesis of the (*E*)-vinylacetate functionality,[3c] which is present in the C-10 side chain of **1** and **2**. The Williams group has developed an effective method to solve this problem by means of a Wittig reaction with ylide **6** as illustrated in eq 1.[5]



(1)

Based on the above facets, the proposed retrosynthetic approach to **2**, shown in Scheme 2, exploits the synthetic methods developed by the two groups. The side chain functionality was anticipated to be introduced into the tricyclic core **7** using cuprate conjugate addition followed by alkylation of the resulting enolate. The tricyclic core had been previously generated in racemic form by an intramolecular hetero-Diels-Alder reaction from the enal **8**.[3c] The cycloheptadiene ring in **9** was readily generated from a [4 + 3] cycloaddition between the diene **10** and the vinyldiazoacetate **11a** (X = H).[3c] However, to apply this synthetic approach to the enantioselective synthesis of the natural product target, the initial [4 + 3] cycloaddition would need to be conducted in an enantioselective manner. Once the quaternary stereogenic center in **9** has been set, the control of the remaining stereocenters should be relatively straightforward. Preliminary studies on Rh_2(*S*-DOSP)$_4$-catalyzed cycloaddition with the vinyldiazoacetate **11a** (X = H) were not very promising, as the highest enantioselectivity that could be obtained in this type of cycloaddition was only 63% ee.[3c] If the enantioselective [4 + 3] cycloaddition between 3-siloxy-2-diazobutenoate **11c** (X = OTBS) and pyrroles[4c] could be extended to regular dienes, then this could be an acceptable solution for an asymmetric entry into the necessary cycloheptadiene systems. Therefore, the first stage of this investigation was to determine the scope of this enantioselective transformation with model dienes.

The reaction of 3-siloxy-2-diazobutenoate **11c** with trans-piperylene was used to optimize the conditions for the [4 + 3] cycloadditions (Table 1). The Rh_2(*S*-DOSP)$_4$ catalyzed reaction at room temperature, generated the desired product **12** in high yield but with poor enantioselectivity (38% ee). The enantioselectivity of **12** could be improved to 53% ee by conducting the reaction at −26 °C but under these conditions the yield dropped to 35%. In contrast, the Rh_2(*S*-PTAD)$_4$ catalyzed reaction at room temperature gave **12** in 78% yield and 86% ee. At −26 °C, the enantioselectivity improved to 95% ee and the yield was 88%. As previously observed in the Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-DOSP)$_4$ catalyzed reactions of **11c**,[4c] both catalysts preferentially form the same enantiomer.

The Rh_2(*S*-PTAD)$_4$ catalyzed reactions of **11c** could be conducted with a variety of dienes and the results are summarized in Table 3. In all the systems tested, the cycloadducts are formed in good yields (57–86%) and with high enantioselectivities (87–98% ee). The reaction with cis-piperylene generates the cycloheptadiene **13**, the opposite enantiomer to the product generated from transpiperylene. Even though the cycloadduct **18**, from reaction with 4-methyl-1,3-pentadiene, is not chiral, a successful reaction with this substrate was of importance

for this endeavor, as a 4-substituted-1,3-diene was required for total synthesis studies (see table 3 below).

The absolute configuration of the products **12–17** has been assigned using the predictive model for cyclopropanation with donor/acceptor carbenoids[3b,6] combined with the catalyst model developed by Hashimoto[7] for related phthalimido carboxylate rhodium catalysts. This model correctly predicted the absolute configuration of the [4 + 3] cycloadducts from the Rh_2(*S*-PTAD)$_4$ catalyzed reactions of 3-siloxy-2-diazobutenoate **11c** with pyrroles.[4c] In the model shown in Scheme 3, the vinylcarbenoid in the complex **19** aligns with the bulky group (OTBS) away from the phthalimido groups. The diene approaches from the front face to generate the divinylcyclopropane **20**, which then undergoes the Cope rearrangement through a boat transition state to form **21**. Evidence to confirm the accuracy of the predictive model was obtained by conversion of the cycloheptadiene **14** to (S)-phenylsuccinic acid by an oxidative ozonolysis of the two double bonds in **14**.[4b]

Our focus then turned to the examination of the [4 + 3] cycloaddition with the actual diene **10** required for the total synthesis (Table 3). Earlier studies[6c] had shown that the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **10** with the vinyldiazoacetate **11a** did not give the cycloheptadiene **22a** with high asymmetric induction. A similar reaction of **11a** catalyzed by Rh_2(*S*-PTAD)$_4$ failed to enhance the enantioselectivity (entry 2). Altering the methyl ester to a *tert*-butyl ester as in **11b** had a considerable effect on the enantioselectivity. The reaction of **11b** with **10** catalyzed by Rh_2(*S*-DOSP)$_4$ gave **22b** in only 5% ee (entry 3), whereas the Rh_2(*S*-PTAD)$_4$ catalyzed reaction gave **22b** in 57% ee (entry 4). Significantly better results were obtained with the siloxyvinyldiazoacetate **11c**. Even though the Rh_2(*S*-DOSP)$_4$ catalyzed reaction of **11c** gave the [4 + 3] cycloadduct **22c** with only moderate enantioselectivity (45% ee, entry 5), the Rh_2(*S*-PTAD)$_4$ catalyzed reaction gave **22c** in 67% yield and 90% ee (entry 7). This asymmetric transformation sets up the crucial quaternary stereogenic center required to control the remaining stereocenters in the synthesis.

The model studies showed that an enantioselective [4 + 3] cycloaddition is a viable approach for the total synthesis of either (−)-vibsanin E (**1**) and/or (−)-5-*epi*-vibsanin E (**2**). The predictive model (Scheme 4) indicates that the enantiomeric catalyst Rh_2(*R*-PTAD)$_4$ will be required in the key reaction. The [4 + 3] cycloaddition between diene **10** and **11c** could be conveniently conducted on a ten gram scale with Rh_2(*R*-PTAD)$_4$ loading as low as 0.5 mol % to generate the cycloheptadiene **23** in 67% yield with 90% ee. The siloxy group in **23** was removed and the resulting enol was converted to the triflate, and then reduced under palladium-catalyzed conditions to form **24**. The generation of the tricyclic core **7** from **24** was achieved using a similar sequence to the one that had been previously used in the racemic series.[3c] Conversion of the unsaturated ester in **24** to the aldehyde followed by a Lewis-acid catalyzed hetero-Diels-Alder reaction generated the tricycle **25** in 77% overall yield. Reduction of the enol ether in **25** under acidic conditions followed by allylic oxidation generated the key tricyclic enone **7**. This material could be enriched by a single recrystallization from hexanes (75% recovery) or by preparative HPLC using a chiral stationary phase.

Much of the previous difficulties encountered with the synthesis of **1** and **2** arose due to complications with introduction of the side chains.[3] An obvious solution to these problems, starting from bicycle **7**, was utilization of tandem conjugate addition/alkylation chemistry. However, the most applicable reagents (vinyl, allyl, etc.) failed to undergo the 1,4-addition, presumably due to the presence of the sterically crowded quaternary center at the γ-position. The only reported successful conjugated addition to **7** occurred for a methyl group, which did generate the desired 10-β stereochemistry.[3c] These results led to the expectation that only a highly electron rich cuprate would facilitate the conjugate addition, but the only functionalized system fitting this criterion are the α-oxa methylene anions (i.e. $MOMOCH_2Li$ derived from

$MOMOCH_2SnBu_3$).[8] Initial attempts to drive the 1,4-addition failed; however, addition of the activator, TMSCl,[9] promoted the reaction with the desired regiochemistry of the silyl enol ether **26** in excellent yield (Scheme 5).

Attempts to trap the *in situ* enolate, derived from the cuprate addition with various allyl electrophiles failed. Treatment of **26** with methyl lithium to generate the desired regioisomer of the enolate followed by quenching with allyl bromide afforded the *O*-allylated material **27** in 74% yield. This reaction was very effective at relatively small scale [0.6 mmol (**26**)], but upon scale-up, significant amounts of the undesired bridgehead C-allylated material was formed, which was also observed in the subsequent Clasien rearrangement below. Microwave promoted Claisen rearrangement of **27** afforded the *syn*- and *anti*-isomeric products, **28** (41%) and **29** (11%), respectively. Acetal deprotection proceeded when gently heated in aqueous methanolic acid, albeit with slight epimerization. Swern oxidation and subsequent Wacker oxidation afforded the diketoaldehyde **30** in 20% yield over three steps. Treatment of **30** with ylide **6**,[5] the Anders-Gaβner variant on the Wittig reaction,[10] produced 5-*epi*-vibsanin E (**2**) [11] in 26% yield (Scheme 5).

In conclusion, considerable effort has been exerted in the pursuit of natural products containing densely functionalized fused seven-membered rings (e.g. the guanacastepenes).[12] The challenges associated with such synthetic campaigns has been a driving force for the development of a number of new synthetic strategies, The total synthesis of 5-*epi*-vibsanin E (**2**), efficiently synthesized in 18 steps, is a further exemplar to this cause, in that, the synthesis combines asymmetric rhodium-catalyzed [4 + 3] cycloaddition methodology to rapidly generate the tricyclic core paving the road for an effective end game strategy to introduce the remaining side-chains.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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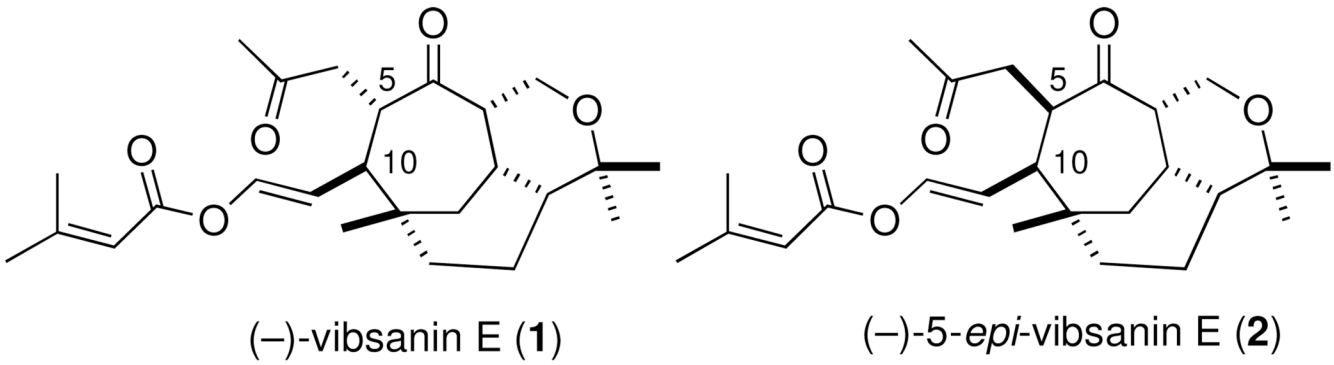
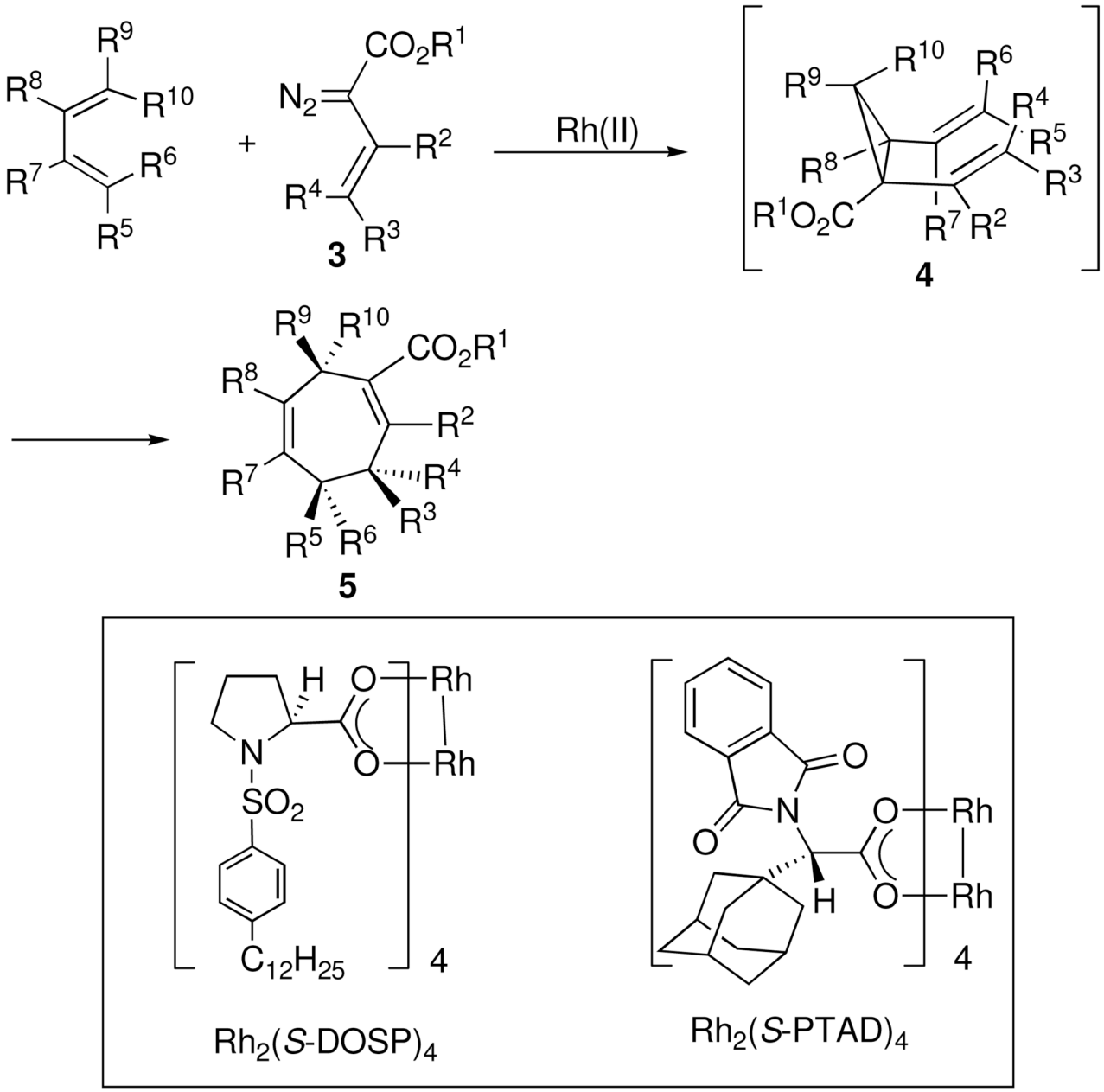
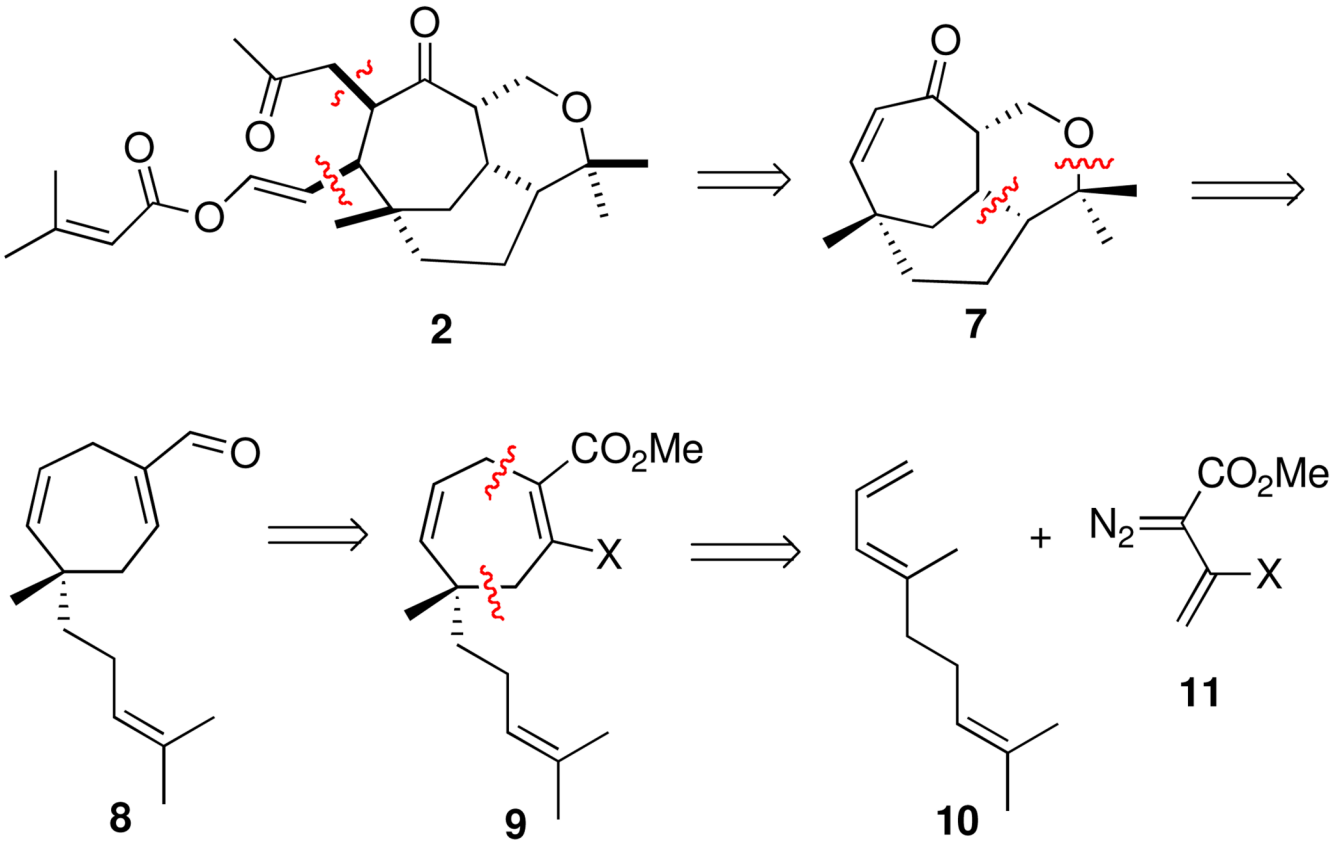


Figure 1.



Scheme 1.



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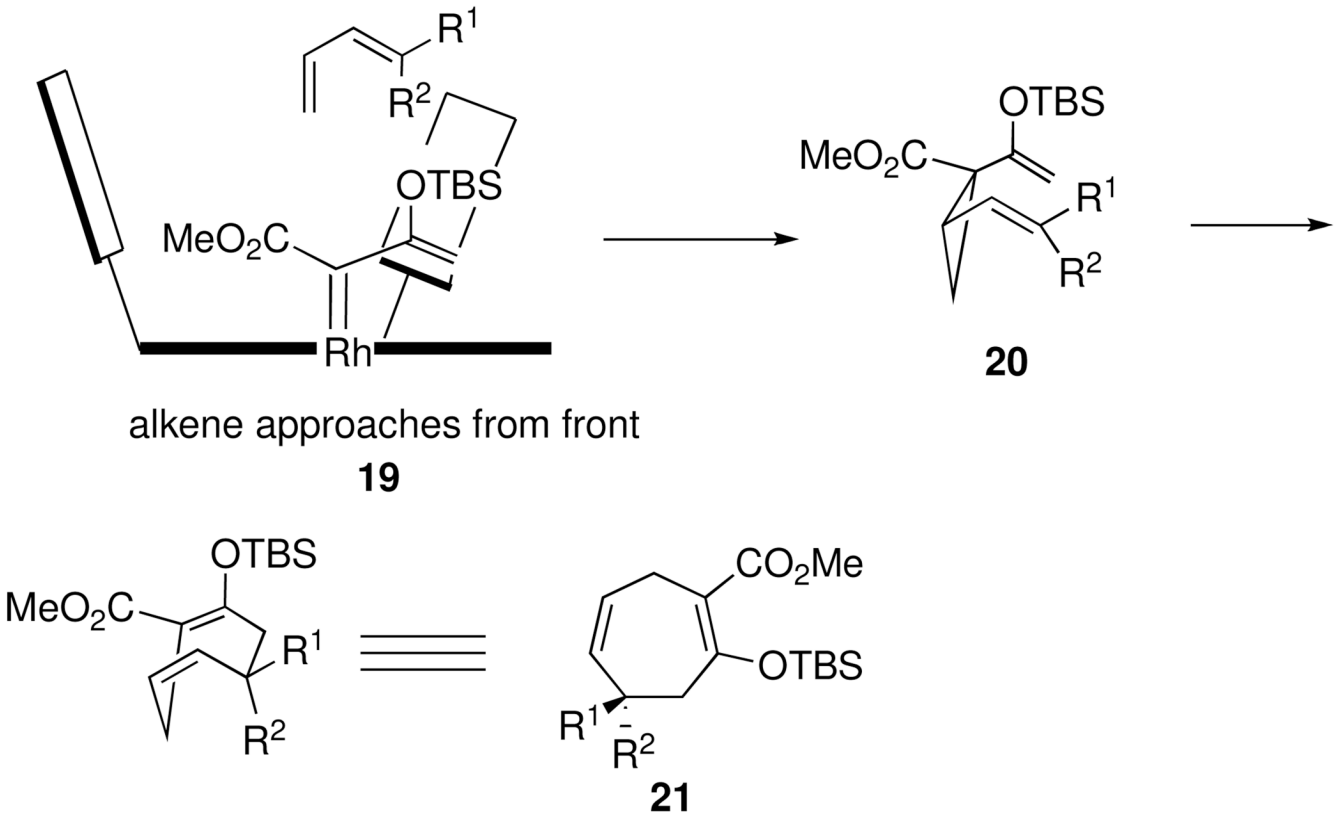

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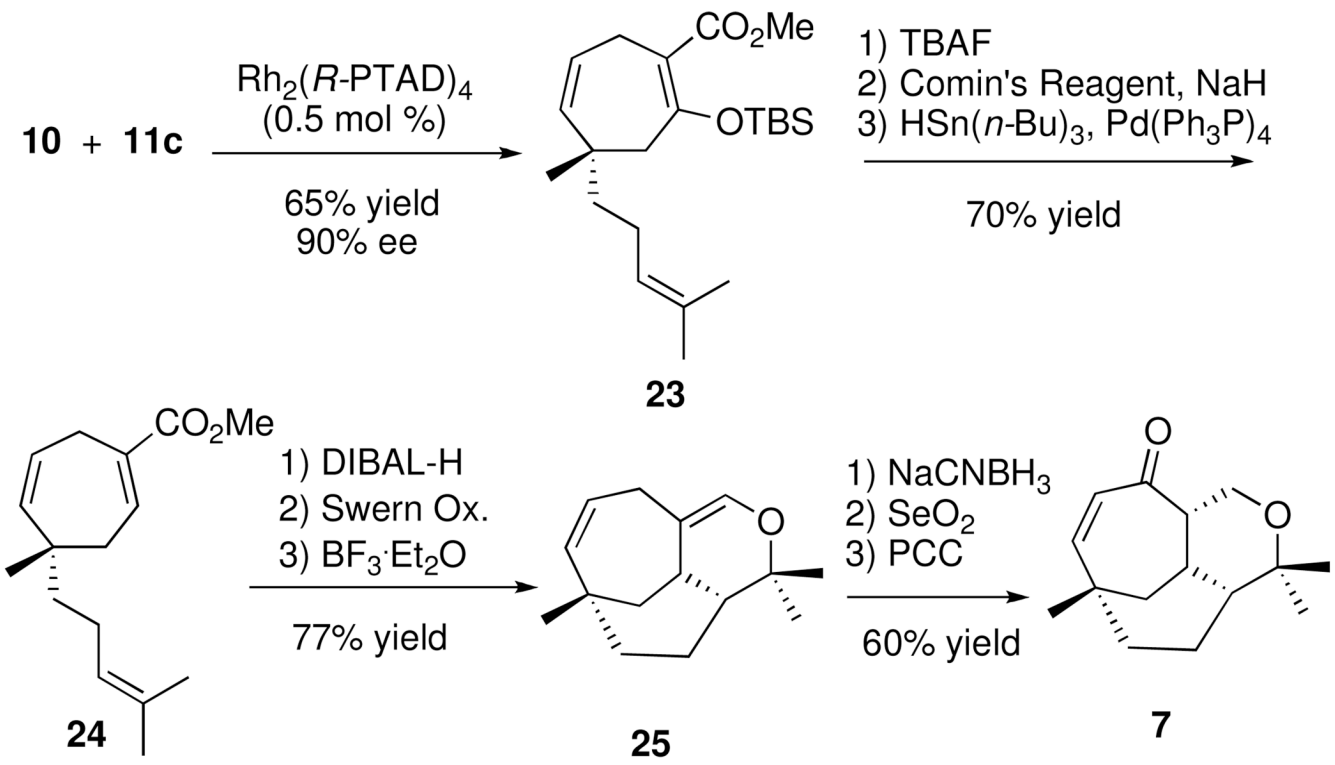

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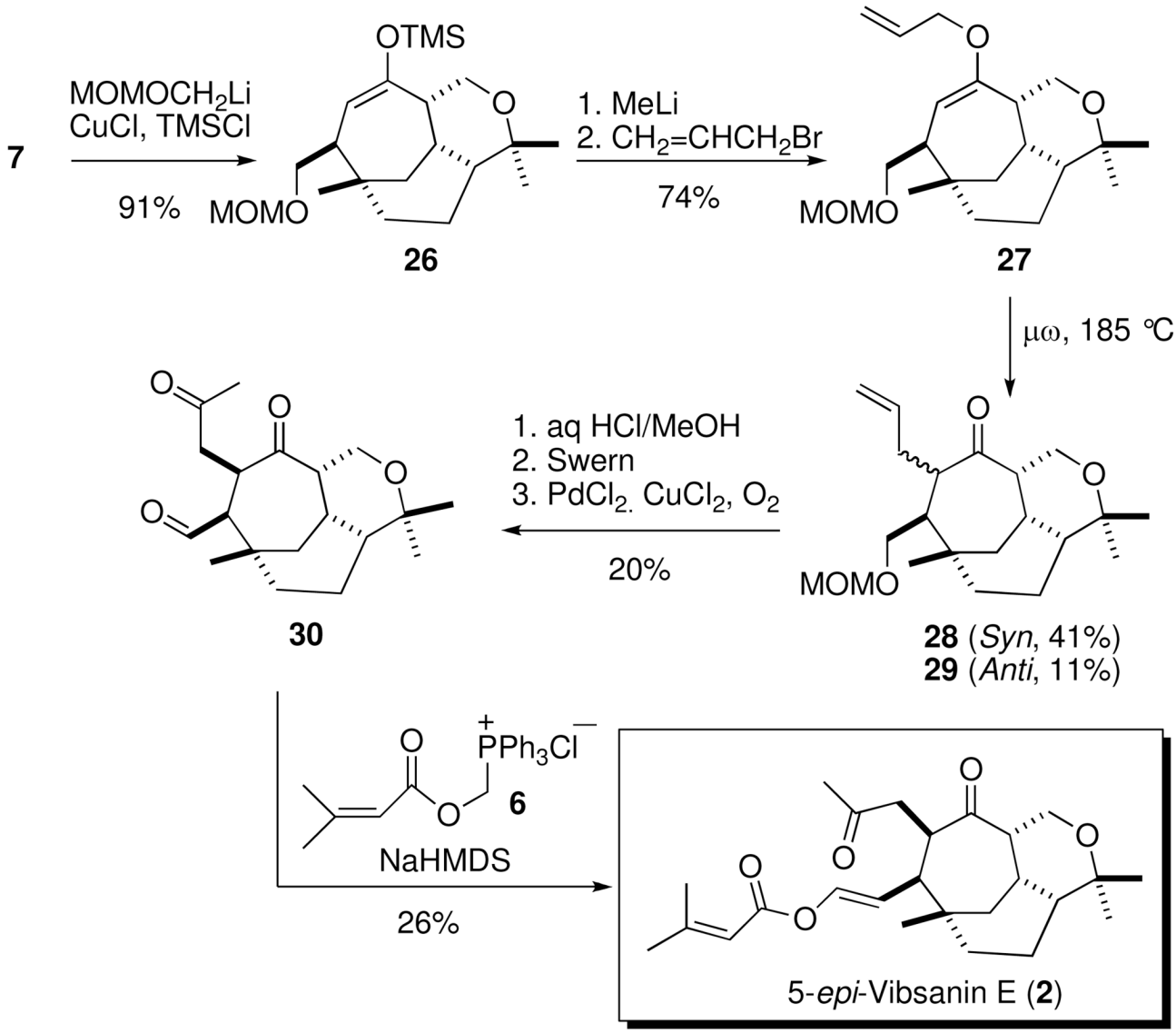
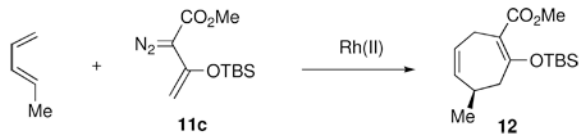


Scheme 5.

Table 1

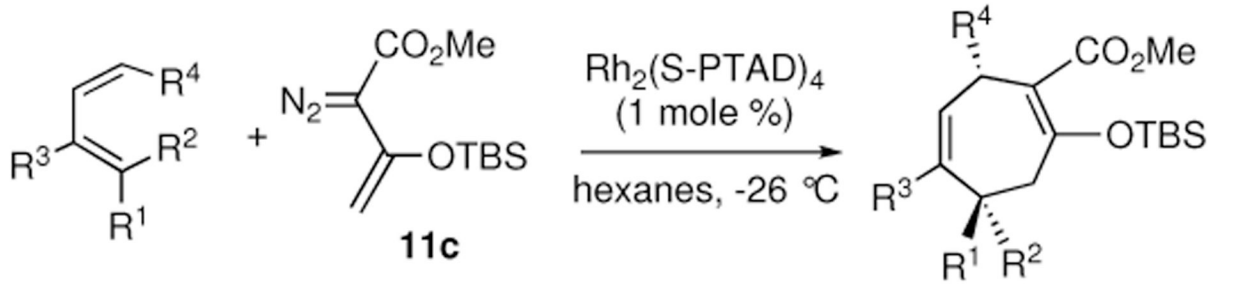
Optimization of the enantioselective [4 + 3] cycloaddition

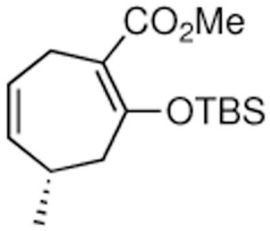


Rh(II)	temp (°C)	yield(%)	ee (%)
Rh_2(S-DOSP)$_4$	23	85	38
Rh_2(S-DOSP)$_4$	−26	35	53
Rh_2(S-PTAD)$_4$	23	78	86
Rh_2(S-PTAD)$_4$	−26	88	95

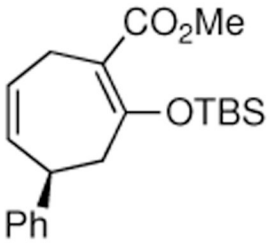
Table 2

[4 + 3] Cycloadditions between **11c** and dienes

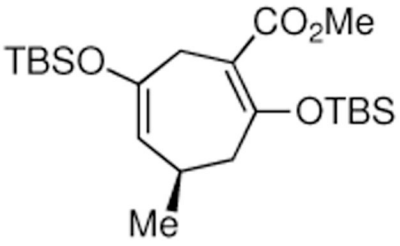




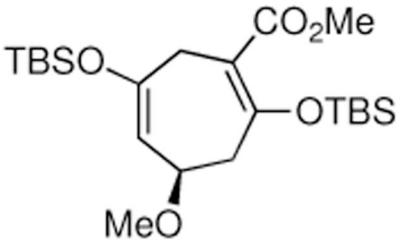
13
80% yield
87% ee



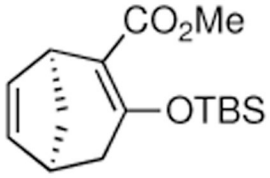
14
82% yield
95% ee



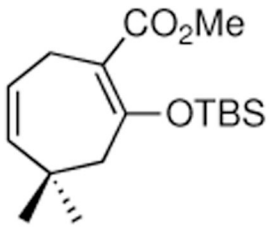
15
70% yield
99% ee



16
63% yield
95% ee



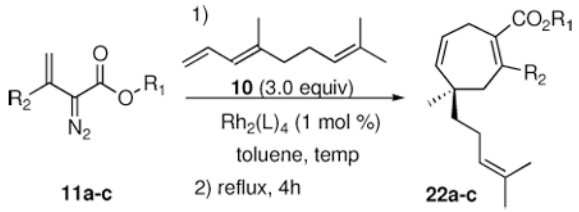
17
86% yield
92% ee



18
57% yield

Table 3

Enantioselective [4 + 3] cycloadditions with diene **10**



entry	$Rh_2(L)_4$	R_1	R_2	temp (°C)	product	yield (%)	ee (%)
1	Rh_2(*S*-DOSP)$_4$	CH_3	H	rt	**22a**	62	50
2	Rh_2(*S*-PTAD)$_4$	CH_3	H	rt	**22a**	67	40
3	Rh_2(*S*-DOSP)$_4$	*t*-Bu	H	rt	**22b**	60	5
4	Rh_2(*S*-PTAD)$_4$	*t*-Bu	H	rt	**22b**	63	57
5	Rh_2(*S*-DOSP)$_4$	CH_3	OTBS	−78 to rt	**22c**	55	45
6	Rh_2(*S*-PTAD)$_4$	CH_3	OTBS	−20 to −15	**22c**	55	91
7	Rh_2(*S*-PTAD)$_4$	CH_3	OTBS	−10	**22c**	67	90
8	Rh_2(*S*-PTAD)$_4$	CH_3	OTBS	0 to 5	**22c**	70	87