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Development of Domino Processes by Using 7-Silylcycloheptatrienes and Its Analogues

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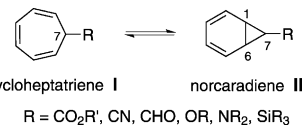
Abstract: 7-Silyl- and 7-silylmethylcycloheptatrienes were shown to react with acylnitroso reagents at room temperature, through their norcaradiene forms, to generate the corresponding cycloadducts **5a–b** and **6a–b** as single diastereomers. The course of the reaction was dramatically modified by changing the reaction conditions. Using a polar medium, functionalized cyclohexa-1,3-dienes **7a–b** and bicyclic compounds **13a–b** were instead generated, incorporating one or two amino groups. Similar behavior was observed by using other dienophiles, including triazolinedione, but also activated aldehydes and ketones. A tentative mechanism has been proposed to rationalize the formation of both classes of products that relies on a domino process involving four consecutive elementary steps, in this order: 1) electrocyclic process, 2) hetero-Diels–Alder reaction, 3) cyclopropane ring opening, and 4) hetero-Diels–Alder reaction. Trapping of the cationic intermediate and isolation of the primary cycloadduct provide support for this hypothesis. An enantioselective version of the cascade using cycloheptatriene **4b** and aldehydes and ketones, under copper(II) catalysis was also carried out, leading to cyclohexa-1,3-dienes **21**, **28**, and **30** with enantioselectivities up to 93% *ee*. Finally, elaboration of the intermediates above has been carried out, opening a straightforward access to sugar mimics **42–43** and complex polycyclic systems **36** and **39**.

Keywords: cycloaddition · diastereoselectivity · domino reactions · fused-ring systems · medium-ring compounds

Introduction

Valence isomerism between cycloheptatriene and norcaradiene has been studied for more than 40 years.[1] This equilibrium encompasses two successive dynamic processes, including a valence bond isomerization and a thermally allowed disrotatory electrocyclic cyclopropane ring opening. The nature of the substituents at C-7 has been shown to influence the position of this equilibrium and subsequently the relative population of both isomers. Electron-withdrawing substituents (R = CN, CO_2R, CHO, etc.) tend to shift the equilibrium toward the norcaradiene form, whereas π-electron-donating groups (OR, NR_2) tend to favor the cycloheptatriene (Scheme 1).[2]

Charge-transfer complexes between the cyclopropane moiety and substituents as well as HOMO–LUMO interactions have been invoked to rationalize these experimental observations.[3] For instance, the predominance of the norcaradiene form when a carboxylic acid group is located at C-7 could be explained by an overlap between the Walsh orbital[4] (HOMO) of the cyclopropane and the π* orbital (LUMO) of the electron-withdrawing substituent, resulting in a lengthening of C1–C7 and C6–C7 bonds and shortening of the C1–C6 bond. This is supported by X-ray studies of a simplified COOH substituted cyclopropane model with vicinal and distal bond lengths of 1.53 and 1.46 Å, respectively.[5] Although the norcaradiene form may be detected through standard spectroscopic methods, its presence is more easily confirmed by carrying out a Diels–Alder reaction on the mixture at equilibrium.[6] Early work by Ashe[7] thus showed that heating 7-trimethylsilylcycloheptatriene (**1**) and acetylene dicarboxylate at 160 °C led to the expected [4+2] cycloaddition product **2** along with a second cycloadduct **3** issued from a [1,5]-sigmatropic rearrangement, thus demonstrating that norcaradiene is the reacting species at high temperature (Scheme 2). The π-acceptor character more than the σ-donating properties of the SiR_3 group are probably reflected in this experiment.[8]



Scheme 1. Cycloheptatriene–norcaradiene equilibrium.

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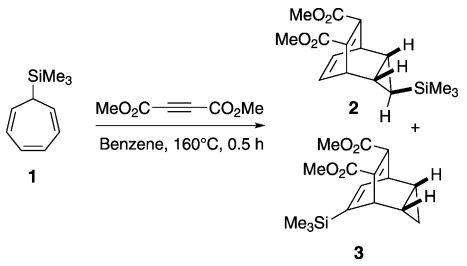


Scheme 2. Diels–Alder reaction of 7-silylcycloheptatriene **1**.

Although many studies have been carried out by varying the nature of the substituents at C-7, we noticed that very little was known about cycloheptatrienes substituted at C-7 by a silicon group. In the course of our ongoing studies on silylated polyenes[9] and convinced that the synthetic value of silylcycloheptatrienes had so far been underestimated, we initiated a series of studies on cycloheptatrienes substituted at C-7 by a silicon or a silylmethyl group.[10] It is noteworthy that a silicon group can be regarded as a masked hydroxyl group,[11] which is crucial in this context because OR and a SiR_3 substituents should influence the above equilibrium with adverse effects. During our preliminary studies, we discovered during acyl nitroso cycloadditions onto cycloheptatrienes **I** (Figure 1), an unusual domino process leading,

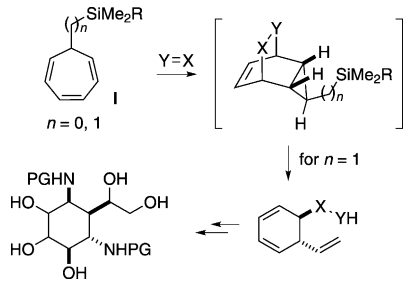
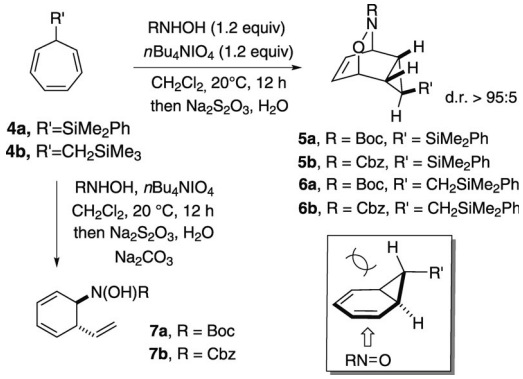


Figure 1. Elaboration of silylcycloheptatrienes into sugar mimics.

after further functionalization, to carbasugar type products.[12] In this report, we provide a full account of our work and describe an extension to cycloaddition reactions involving aldehydes and ketones. Mechanistic aspects of these intriguing transformations are also discussed.

Results and Discussion

Cycloadditions of silylcycloheptatrienes 4a–b with acylnitroso reagents: The synthesis of silylcycloheptatriene precursors **4a–b** was carried out through direct silylation of tropylium tetrafluoroborate using $(PhMe_2Si)_2Zn$[13] or the Grignard reagent Me_3SiCH_2MgBr.[14] During our preliminary investigations,[12] we observed that highly reactive acyl nitroso reagents[15] efficiently trapped the norcaradiene valence isomer of **4a** and **4b**, to provide the resulting cycloadducts **5a–b** and **6a–b** in good yield as a single diastereoisomer, regardless of the reaction conditions or which nitroso reagent was used (Scheme 3). Structures of **5** and **6** were as-

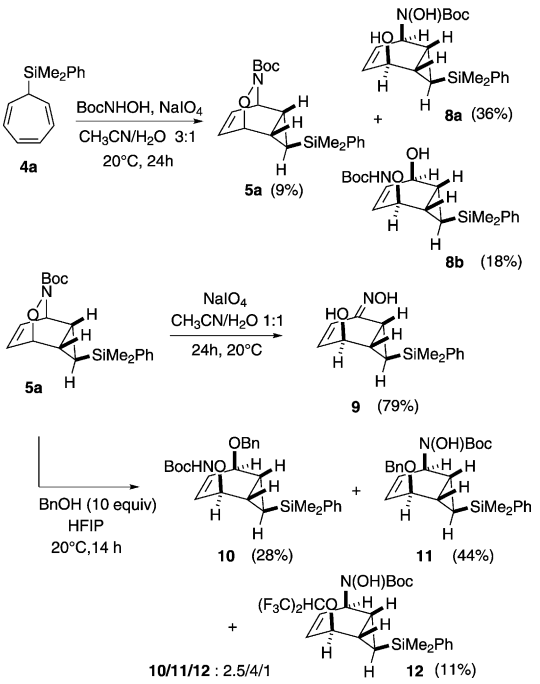


Scheme 3. Acylnitroso cycloadditions onto 7-silylcycloheptatrienes **4a–b**.

signed through ^1H NMR analysis and X-ray diffraction studies, which established unambiguously that the reactivity of **4a** and **4b** in the cycloaddition processes is expressed through the norcaradiene form.

The norcaradiene behaves as a 1,3-diene and exhibits higher reactivity than the cycloheptatriene form in cycloaddition processes at room temperature.[16] No [1,5]-sigmatropy was observed under these mild conditions, which led exclusively to the stereoisomer as shown, resulting from an approach of the nitroso reagent *anti* relative to the cyclopropane moiety with a silicon group in the pseudo-equatorial position. Interestingly, **4b** behaved differently to **4a**. When the workup of the cycloaddition reaction was slightly modified by adding $Na_2S_2O_3$ and Na_2CO_3 (to remove the excess of oxidant), instead of $Na_2S_2O_3$ alone, the exclusive formation of cyclohexa-1,3-dienes **7a–b** was observed. Such 1,2-difunctionalized cyclohexadienes are very useful in synthesis and are generally accessible through enzymatic oxidation (*pseudomonas putida*) of the corresponding arenes.[17]

The formation of **7a–b** may be rationalized by invoking a cyclopropane ring opening triggered by cleavage of the allylic C–O bond (see below).[15g–h] Such cleavage is easy under polar conditions[18] as shown by the formation of compounds **8a–b** during the cycloaddition between Boc-nitroso and cycloheptatriene **4a** in CH_3CN/H_2O (Scheme 4). This is further supported by the facile ring opening of cyclopropane **5a** into **8a–b** with $NaBF_4$ in CH_3CN/H_2O. When the same reaction was repeated without $NaBF_4$, **5a** was recovered unchanged, indicating that a simple salt effect[19] is sufficient to promote the cleavage of both the allylic C–O and/or C–N bonds. Similarly, treatment of **5a** with $NaIO_4$ in the same medium led to both ring opening and oxidation of the hydroxylamine to afford the corresponding oxime **9** in good yield. It is finally noteworthy that, in each case, a single diastereoisomer is observed, implying that the nucleophile (H_2O) is probably directed by the resident heteroatoms in a suprafacial manner through hydrogen bonding.[20] The same

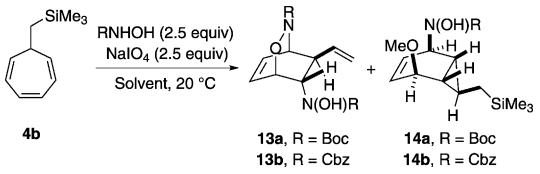


Scheme 4. Salt effects during acylnitroso cycloadditions onto 7-silylcycloheptatriene.

trend was observed with cycloadducts **6**, which readily opened to form **7**, in the presence of $NaBF_4$ or $LiClO_4$ in a 1:1 CH_3CN/H_2O mixture. We also investigated the possibility of extending this chemistry to other nucleophiles, including sugars, which would allow access to carba-C-disaccharides. Unfortunately numerous attempts led, in most cases, to complex mixtures due to concomitant C–O and C–N bond cleavage. For instance, the ring opening of cycloadduct **5a** with BnOH as a nucleophile and HFIP as an ionizing solvent[21] led to the formation of a mixture of three products **10**–**12**, the first two resulting respectively from the cleavage of the C–O and C–N bonds, followed by a stereoselective attack of the putative carbocationic species with BnOH. Surprisingly, a small amount of **12** was also formed as a result of trapping of the carbocation by the poorly nucleophilic HFIP.

Similarly, when **4b** was treated with an excess of BocNHOH or CbzNHOH and $NaIO_4$ in a $MeOH/H_2O$ mixture, cycloadducts **13a**–**b** were formed along with a minor amount of the ring-opened products **14a**–**b**, issued from cleavage of the C–O bond and attack of MeOH as a nucleophile (Table 1). As above, NOESY experiments showed that a single isomer was formed from methanol attacking *syn* relative to the alkoxy amino group. It is noteworthy that analysis of **6b** in solution in MeOH by using mass spectrometry revealed the appearance of a peak corresponding to **6b** (*m*/*z* 344.1685) and a second (*m*/*z* 396.1794) corresponding to **14b**, likely as a result of the ring opening of **6b** mediated by Na^+ ions present in the spectrometer probe, followed by nucleophilic trapping with MeOH (see the Supporting Information). The formation of cycloadducts **13a**–**b** is quite remarkable, with the formation, in a single operation from simple cycloheptatriene **4b**, of a bicyclic system bearing four stereogenic centers, with complete regio- and diastereocontrol. A survey of the reaction conditions leading to the mixture of products **13** and **14** was carried out and is summarized in Table 1. Lower amounts of water relative to MeOH led to larger amounts of the cycloadduct **13a**. Predictably, when acetonitrile was used, no trace of the ring opening product **14a** was observed (Table 1, entry 5).

Table 1. Hetero-Diels–Alder between **4b** and RNHOH in various solvents.



Entry	R in RNHOH	Solvents	*t* [h]	**13**/**14** ratio[a]	Yield [%][b]
1	Boc	$MeOH/H_2O$ (1:1)	48	4:1	50
2	Boc	$MeOH/H_2O$ (2:1)	48	7:1	46
3	Boc	$MeOH/H_2O$ (3:1)	12	8:1	57
4	Cbz	$MeOH/H_2O$ (3:1)	12	8:1	59
5	Boc	CH_3CN/H_2O (2:1)	48	1:0	40

[a] Estimated ratio by ^1H NMR analysis of the crude reaction mixture. [b] Isolated yield of the major compound **13**.

The formation of **13** and **14** may be rationalized by invoking the facile cleavage of the allylic C–O (or in some cases the C–N bond) under the reaction conditions, which triggers the cyclopropane ring opening through a cationic pathway.[22] Norcaradienes **6a**–**b** are the key intermediates in the domino process. We observed in the X-ray structure of **6b**, that cyclopropane C1–C2 bond was slightly longer than the C1–C3 bond (Figure 2), probably as a result of the higher electronegativity of the oxygen relative to nitrogen. A polar medium and the presence of a cation that may coordinate

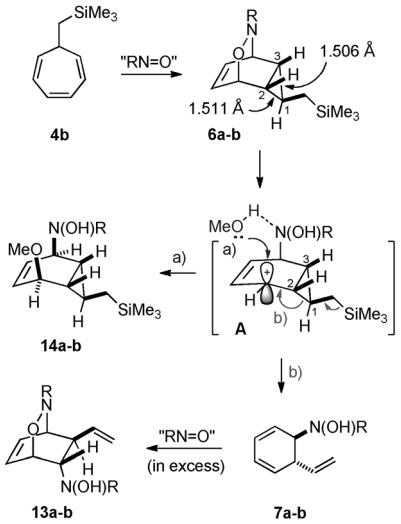
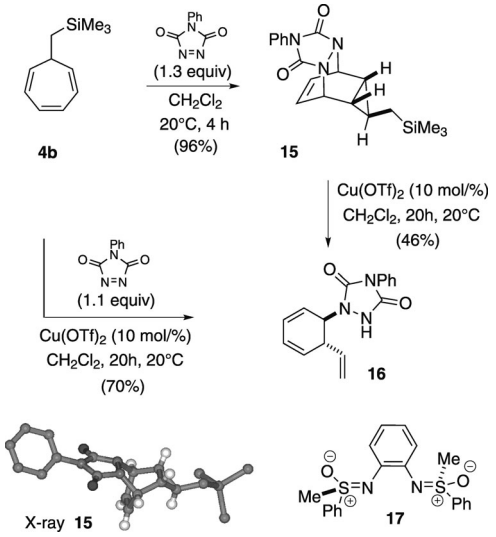


Figure 2. Tentative mechanism for the cascade process.

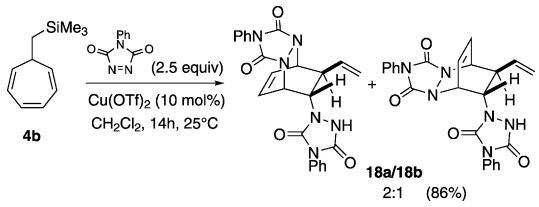
with the oxygen atom, trigger the cleavage of the C–O bond, leading to the formation of a carbocation intermediate.[15g,23] The latter may be trapped by either the solvent or any nucleophile in the reaction mixture to provide **8**–**12** from **4a** (Scheme 4) and **14** from **4b** (Table 1). In the case of silylmethylcyclopropane **4b**, suitable alignment between the antiperiplanar C–Si bond and C1–C2–C$^+$ initiates the cyclopropane ring opening with loss of the silicon group to afford cyclohexa-1,3-dienes **7a**–**b**. The generation of a putative carbocation such as **A** as an intermediate is favored with precursors **6** because the electron-rich C–Si bond offers a stabilization of the positive charge through a "vinylogous β-silicon effect",[24] explaining the low amount of **14a**–**b** formed upon hetero-Diels–Alder reaction with **4b** in polar medium (Figure 2). Silylmethylcyclopropanes are well-known to open under electrophilic or acidic activations.[22,25] In contrast, such a ring-opening is not favored when the silyl group is directly linked to the cyclopropane, as in **5a**–**b**. When an excess of the nitroso reagent was used, dienes **7a**–**b**, generated in situ, react as dienophiles, offering straightforward access to highly functionalized cycloadducts such as **13a**–**b**. The latter are formed through an unprecedented hetero-domino process,[26a] involving consecutive electrocyclic process/hetero-Diels–Alder reaction/cyclopropane ring opening/hetero-Diels–Alder reaction.[15a,26b–c]

Cycloadditions of silylcycloheptatriene 4b with triazolinedione: The hetero-domino process depicted above (Figure 2) can give rise to highly functionalized compounds, starting from the readily available silylcycloheptatriene **4b**. For instance, hetero-Diels–Alder reaction between **4b** and triazolinedione[27] led to the expected norcaradiene cycloadduct **15** as a single *endo*-isomer (X-ray) (Scheme 5). When treated with $Cu(OTf)_2$, **15** led, after cleavage of the C–N bond and subsequent cyclopropane ring opening, to the cyclohexa-1,3-diene **16** in modest yield.[28] Formation of **16** could, however, be carried out, in better yield, in one pot by simple treatment of **4b** with 1.1 equivalents of triazolinedione and a catalytic amount of $Cu(OTf)_2$ (10 mol%). It is noteworthy that, after 10 min at 20°C, cycloadduct **15** and diene **16** were both present in the medium, showing that **15** was again the key intermediate in the process, further supporting the mechanism proposed in Figure 2.



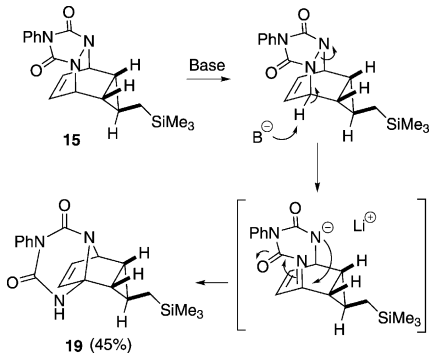
Scheme 5. Hetero-Diels–Alder between **4b** and triazolinedione.

Based on the assumption that the allylic bond cleavage was triggered by the Lewis acidic $Cu(OTf)_2$, we repeated the reaction by using chiral ligands (12 mol%), such as bisoxazolines and Bolm Bis(sulfoxymine) **17**,[29] which are known to mediate copper-catalyzed asymmetric processes. Whereas bisoxazolines led to no enantioselectivity, **16** was obtained from **4b** in 70% yield and 10% enantiomeric exess with ligand **17**, thus demonstrating that desymmetrization of substrates such as **15** is feasible. Compound **4b** was also treated with an excess of triazolinedione, which led, following the domino reaction depicted in Figure 2, to the biscycloadduct as a 2:1 mixture of two separable diastereoisomers **18a** and **18b** (Scheme 6).



Scheme 6. Domino process using **4b** and triazolinedione.

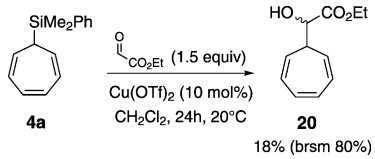
Base-mediated ring opening was also tested as a potent strategy to desymmetrize tetracyclic systems such as **15**. Treatment of **15** with lithium diisopropylamide (LDA) thus provided 2,4-dioxohexahydro-1,3,5-triazine **19** in 45% yield, likely as a result of the unusual base-catalyzed rearrangement[30] depicted in Scheme 7.



Scheme 7. Base-catalyzed rearrangement of norcaradiene-derived urazole **15**.

Cycloadditions of silylcycloheptatrienes 4a–b with aldehydes and ketones: Based on the results discussed above, the reactivity of silylcycloheptatrienes **4a** and **4b** toward aldehydes and ketones was then studied. It was envisioned that **4a** could react through either the cycloheptatriene form as an

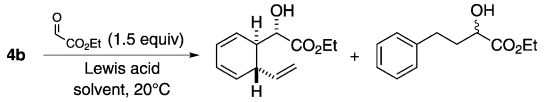
allylsilane, providing Hosomi–Sakurai[31] products, or the norcaradiene form, leading to cycloadducts in the presence of reactive aldehydes. In contrast, **4b**, being a homoallylsilane, Alder-ene as well as Diels–Alder reactions could be envisaged through the cycloheptatriene form, whereas cycloadditions and further ring opening could result from the occurrence of the norcaradiene form. Alternatively, reaction of the norcaradiene silylmethylcyclopropyl moiety with carbonyl groups under acidic conditions with concomitant ring opening cannot be ruled out.[25] Preliminary reactions between **4a** and ethyl glyoxylate afforded, as expected, alcohol **20**, through a Hosomi–Sakurai reaction, albeit in poor yield and stereocontrol (Scheme 8).



Scheme 8. Reaction of **4a** with ethyl glyoxylate.

More interestingly, **4b** was found to react under Lewis acid catalysis[32] with the same glyoxylate to provide separable cyclohexa-1,3-diene **21** and alcohol **22**. A survey of the reactions conditions and catalysts was carried out and the results are summarized in Table 2. Better results were generally obtained when metal triflates were used, with scandium being the best (Table 2, entry 8), leading to **21** as the sole product. Good results were also observed with copper and tin catalysts (Table 2, entries 3 and 7, respectively). Compound **21** was, in all cases, obtained as a single isomer with relative configuration as shown (see below). Anhydrous dichloromethane was found to be the best solvent for these reactions. The formation of **22** was attributed to the presence, in certain cases, of metal triflates containing a higher content of triflic acid. For instance, reacting **4b** with 1.5 equivalents of ethyl glyoxylate and a few drops of triflic acid led to the formation of **21** and **22** after a few minutes, indicating that triflic acid catalyzed the formation of both products. Attempts to extend this reaction to less reactive aldehydes such as benzaldehyde, furfural, or chelating 2-benzyloxyacetaldehyde led to no reaction and recovery of the starting aldehyde, regardless of the catalytic system used, indicating that the process is restricted to aldehydes bearing strongly electron-withdrawing substituents.

Table 2. Reaction of **4b** with ethyl glyoxylate.



Entry	Lewis acid ([mol %])	Solvent	*t* [h]	**21**/**22** ratio[a]	Yield [%][b]
1	$Cu(CH_3CN)_4ClO_4$ (15)	CH_2Cl_2	48	1:1	48
2	$Cu(CH_3CN)_4PF_6$ (15)	CH_2Cl_2	14	1:0.6	69
3	$Cu(OTf)_2$ (15)	CH_2Cl_2	14	9:1	54
4	$Cu(OTf)_2$ (10)	Et_2O	72	4:1	69
5	$Zn(OTf)_2$ (10)	CH_2Cl_2	72	1:1	50
6	$Zn(OTf)_2$ (10)	Et_2O	72	3:2	53
7	$Sn(OTf)_2$ (15)	CH_2Cl_2	16	8.5:1	74
8	$Sc(OTf)_3$ (12)	CH_2Cl_2	14	1:0	65

[a] Estimated ratio by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of **21**+**22**.

We then examined an enantioselective version of the above reaction by varying the nature of the Lewis acids, the ligands associated to the metal, and the solvent used in the reaction. The high reactivity of ethyl glyoxylate compared with benzaldehyde is likely due to the electrophilicity of the former and its ability to chelate the Lewis acidic metal. Metal triflates, including copper, tin, zinc, and scandium have been shown to mediate asymmetric processes in a very efficient manner when associated with chelating ligands, such as bisoxazolines (Box)[33] and bis(sulfoxymines),[29] among others. Preliminary results with $Sc(OTf)_3$ and $Sn(OTf)_2$ in the presence of commercially available bisoxazoline ligands led to no reaction. We thus turned our attention to ligands **23**–**26** (Figure 3) using $Cu(OTf)_2$[34] and $Zn(OTf)_2$[35] as catalysts (Table 3). The reaction was carried out

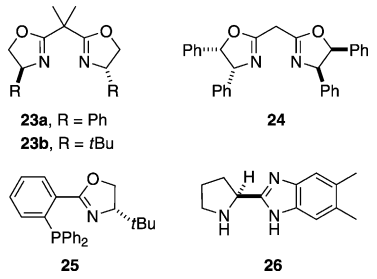
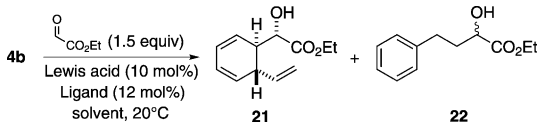


Figure 3. Chiral ligands used for cycloaddition of **4b** with ethyl glyoxylate.

at 20 °C, using 10 mol % catalyst and a slight excess of ligand (12 mol %) to quench traces of triflic acid present in the medium. The best results were observed with copper, which led to an encouraging 93 % *ee* using sterically hindered (*S*,*S*)-Box-*t*Bu **23b** (Table 3, entry 2). The ratio were generally in favor of the cyclohexadienes, when using $Cu(OTf)_2$ (Table 3, entries 1–3, 5, 6, and 10–12), with lower selectivities being observed with zinc. The use of diethyl ether as solvent led to slightly better enantioselectivity than use of dichloromethane, albeit at the expense of yield (Table 3, entry 2 vs. 11). Ligand **26**, recently developed in our laboratory,[36] led to interesting results in terms of yield and enantioselectivity, with better selectivity (82 % *ee*) being obtained at 0 °C (Table 3, entry 6). The absolute configuration of (−)-**21** (obtained with ligand **23b**) was assigned through X-ray structure determination of an intermediate (see below).

Overall, better yields and enantioselectivities for the formation of **21** were observed when using 10 mol % $Cu(OTf)_2$ with 12 mol % ligand. These conditions were then used with

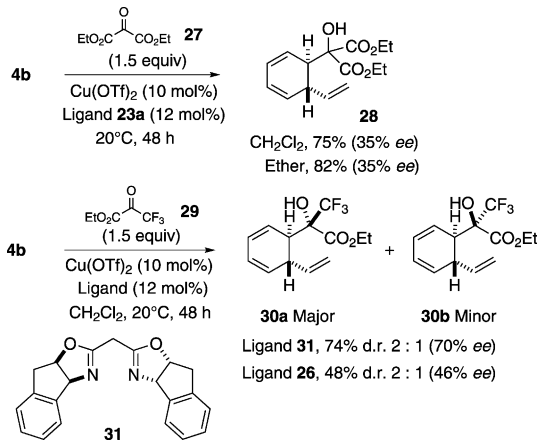
Table 3. Enantioselective reaction of **4b** with ethyl glyoxylate.



Entry	Lewis acid ([mol%])	Ligand	Solvent	**21**/**22** ratio[a]	Yield [%][b]	*ee*[c] **21** [%]
1	$Cu(OTf)_2$ (10)	**23a**	CH_2Cl_2	6:1	52	+31
2	$Cu(OTf)_2$ (10)	**23b**	CH_2Cl_2	10.5:1	60	−93
3	$Cu(OTf)_2$ (10)	**17**	CH_2Cl_2	1:0	57	−63
4	$Cu(OTf)_2$ (10)	**24**	CH_2Cl_2	1:0.6	71	−60
5	$Cu(OTf)_2$ (10)	**25**	CH_2Cl_2	1:0	28	−43
6	$Cu(OTf)_2$ (10)	**26**	CH_2Cl_2	1:0	41	−60
7	$Zn(OTf)_2$ (15)	**23a**	CH_2Cl_2	3:1	35	−5
8	$Zn(OTf)_2$ (10)	**23b**	CH_2Cl_2	2.5:1	15	+15
9	$Sn(OTf)_2$ (10)	**23b**	CH_2Cl_2	–	–	–
10	$Cu(OTf)_2$ (10)	**23b**	$CHCl_3$	1:0	56	−93
11	$Cu(OTf)_2$ (10)	**23b**	Et_2O	1:0	43	−95
12	$Cu(OTf)_2$ (10)	**23b**	$PhCF_3$	1:0	18	−71

[a] Estimated ratio by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of **21**. [c] Enantiomeric excess of **21** was measured by HPLC using a Chiralpak AD-H column (Hexanes/*i*PrOH, 95:5). The sign (−) corresponds to the absolute configuration of **21** drawn above and the sign (+) to the enantiomer.

reactive ketones **27** and **29** (Scheme 9). The reaction was thus found to be effective with ketones bearing electron-withdrawing groups such as CO_2R and CF_3. Reaction of **4b** with ketone **27** led to diene **28** in good isolated yield, with



Scheme 9. Enantioselective reaction of **4b** with ketones **27** and **29**.

modest enantioselectivity, with no trace of the aromatic compound (analogue of **22**). No reaction was, however, observed with $Zn(OTf)_2$. Enantioselectivities up to 50% were obtained by using ligand **23b**, but a large amount of the aromatic alcohol was formed in this case. Better enantioselectivity was obtained with ketone **29**, which has two sterically differentiated substituents. In this case, a 2:1 ratio of diastereoisomers **30a–b** was formed, with the relative configuration as shown. The configuration of the quaternary center was assigned based on the configuration established for **21**, following the transition state model discussed below.[37]

Mechanistic considerations on the cycloaddition between silylcycloheptatriene 4b and aldehydes and ketones: Two different mechanisms may be envisioned to rationalize the formation of the products resulting from the metal-catalyzed reaction of cycloheptatriene **4b** with aldehydes and ketones. The first (Path a, Figure 4) would involve nucleophilic

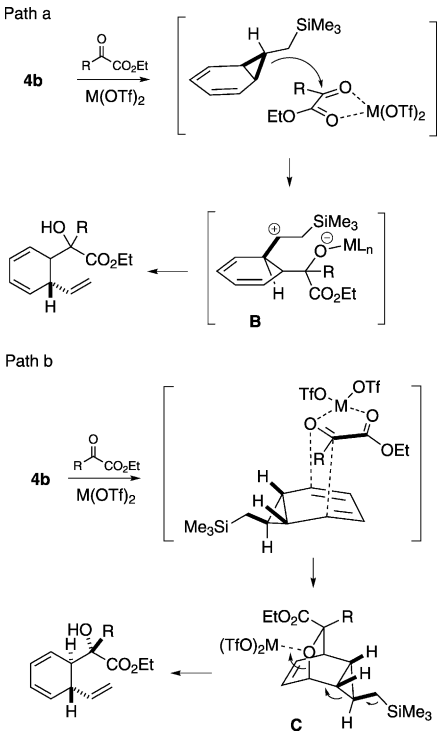
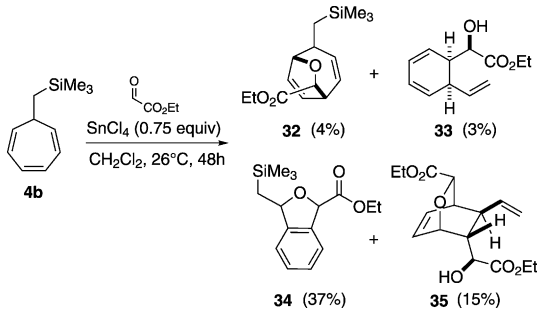


Figure 4. Tentative mechanism for the cascade process between **4b** and aldehydes and ketones.

attack of the silylcyclopropane moiety onto the Lewis acid activated carbonyl group,[22,25] with concomitant cyclopropane ring opening (and formation of a carbocation intermediate **B**). The second approach (Path b) would involve a Diels–Alder cycloaddition, which closely resembles the cascade process proposed above for the formation of dienes **7a–b** (Figure 2). Although it is still premature to draw a definitive mechanism for the formation of **21**, **28**, and **30**, two important points deserve comment. We first observed that ethyl glyoxylate and ketones **27** and **29**, which are known to chelate metal triflate catalysts (through two-point binding), react efficiently with **4b**, whereas benzaldehyde and furfural gave no reaction. This is in good agreement with literature precedent on metal-catalyzed hetero-Diels–Alder reaction, for which **27** and **29** and glyoxylates are frequently used, compared with aryl- and alkyl aldehydes, which are not reactive enough.[38] It was also noticed that, in most cases, the relative configuration of the three stereocenters was completely controlled, giving rise to a single stereoisomer; this would not be expected to be the case with the first mechanism for which open transition states are generally invoked, leading to other stereoisomers. The formation of diene **21**

and analogues should thus occur through a preliminary [4+2] reaction between the norcaradiene form of **4b** and the metal-bound carbonyl group of the dienophile. The dienophile should approach *anti* relative to the cyclopropane ring in an *endo*-mode to provide cycloadduct **C**, which we have not been able to isolate or detect in the reaction mixture. Upon oxygen coordination by the Lewis acid, cleavage of the C–O bond of **C** should occur, triggering the cyclopropane ring opening with concomitant C–Si bond cleavage, to afford the diene with the configuration as shown. The generation of a carbocation intermediate may also be invoked at this stage, although we have not been able to trap it.

Whereas Path a seems disfavored relative to Path b with reactive aldehydes, it is more likely when harder Lewis acids are used. For instance, when the reaction of **4b** and ethyl glyoxylate was mediated by $SnCl_4$ (albeit in substoichiometric amount), we observed the formation of four separable products **32**–**35** in a 1:1:12:5 ratio and an overall yield of 59% after purification (Scheme 10). Compound **32** is



Scheme 10. $SnCl_4$-mediated reaction of **4b** with ethyl glyoxylate.

formed through [4+2] cycloaddition between the glyoxylate and the cycloheptatriene form of **4b**. Bicyclic compound **35** arises from the cycloaddition of a second equivalent of glyoxylate onto the diene **21** generated in situ. It is noteworthy that when the reaction using 0.5 equivalent of $SnCl_4$ was stopped after only 10 min, diene **21** was found to be present in the medium but not **35**, indicating that the former is likely the precursor of **35**. Diene **33** is a diastereoisomer of **21**, the structure of which was unambiguously determined through ^{1}H NMR and NOESY experiments. The formation of **33** and **34** is intriguing because it cannot be explained by Path b alone. It is conceivable that they both originate from nucleophilic attack of the silylcyclopropane moiety onto the $SnCl_4$-activated carbonyl group, as above in Path a, but *syn* to the cyclopropane.[22,25] The resulting carbocation **B** (having a *cis* configuration in this case) would then evolve, either through elimination of the $SiMe_3$ group to give **33** or through cyclization and rearomatization to provide **34**.[39,40]

Finally, with the absolute configuration of **21** established (see below), the topicity of the reaction between **4b** and ketones and aldehydes can be rationalized by invoking an approach of the diene onto the *Si*-face of the keto-ester, forming a square planar copper(II) complex with ligand **23b**

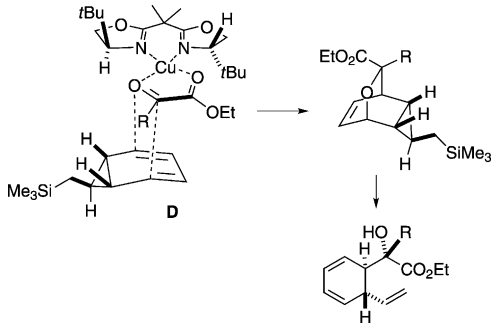
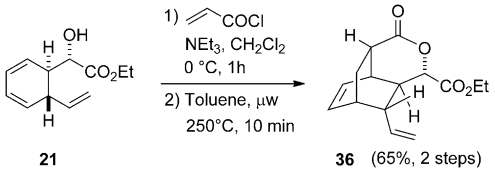


Figure 5. Origin of the enantioselectivity of the Cu^{II}-Box **23b** catalyzed hetero-Diels–Alder reaction between **4b** and ethyl glyoxylate and ketones **27**–**29**.

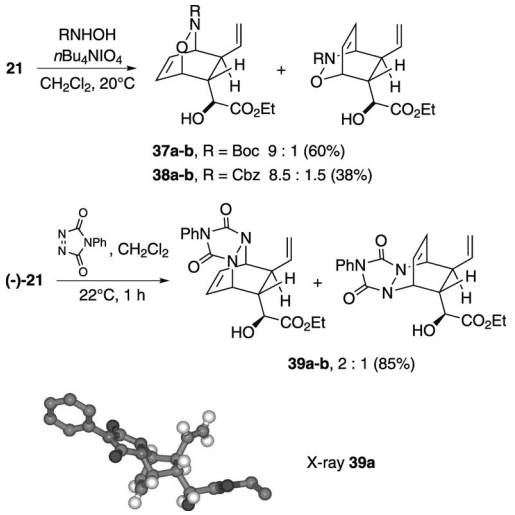
(Figure 5). The alternative approach from the *Re*-face is blocked by the bulky *t*Bu substituent on the ligand.[41] It is also worth adding that opposite stereochemical induction was obtained with ligands **23a** and **23b**, in good agreement with Jørgensen studies on hetero-Diels–Alder processes.[41] This supports our assumption that reaction of **4b** with activated carbonyl compounds occurs through Path b, as depicted in Figure 4.

Further functionalizations of cyclohexa-1,3-dienes; Access to polycyclic systems and amino-carbasugars: Cyclohexa-1,3-dienes such as **21** are useful precursors for the construction of more complex architectures (Scheme 11). For instance, **21** was converted into the corresponding acrylate, which was then heated under microwave irradiation to afford the Diels–Alder adduct **36** as a unique diastereoisomer (established by NOESY experiments, see the Supporting Information) in good overall yield.[42] In comparison, when the reaction was performed in toluene at 125 °C for 46 h, a 8:2 mixture of two regioisomeric cycloadducts was formed.



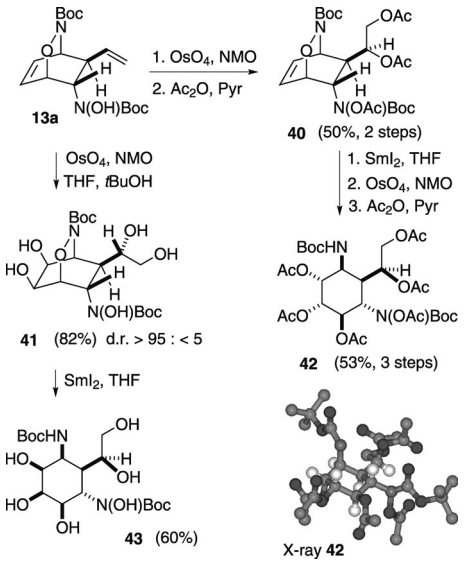
Scheme 11. Synthesis of polycyclic system **36** from diene **21**.

Compound **21** was also submitted to intermolecular cycloaddition with acylnitroso reagents and triazolinedione (Scheme 12). Cycloadducts **37a–b** and **38a–b** were thus obtained with good stereocontrol and moderate yields, with the nitroso reagent adding predominantly *anti* relative to the ester chain. Optically enriched (–)-**21** led, in the presence of triazolinedione, to separable and crystalline cycloadducts **39a–b** in good yield but with poor diastereocontrol. X-ray crystallography of **39a** (shown) and **39b** were used to unambiguously establish the absolute configuration of cyclohexa-1,3-dienes **21** and analogues **28** and **30** (see above).



Scheme 12. Cycloaddition reactions with diene (−)-**21**.

The straightforward synthesis of disubstituted cyclohexa-1,3-dienes also offers access to amino-carbasugars, as illustrated by the two approaches described below (Scheme 13). Cycloadduct **13a**, obtained in a single step from cycloheptatriene **4b** may be osmylated regio- and stereoselectively on the exocyclic double bond to afford **40** after acetylation. Subsequent N−O bond cleavage with SmI_2, followed by a second dihydroxylation and exhaustive acetylation led to protected amino-carba sugar **42** as a single diastereoisomer, the structure of which was determined through X-ray diffraction studies. In parallel, complete dihydroxylation was also carried out under forcing conditions to produce **41** as a single diastereoisomer; the stereochemistry of the latter was assigned based on the relative configuration of **42** and on NOESY experiments. As expected, the osmium reagent selectively approached the *exo* face of the bicyclic system.[43]



Scheme 13. Access to amino-carbasugars from cycloadduct **13a**, obtained in a single step from cycloheptatriene **4b**.

N−O bond cleavage with SmI_2 finally afforded polyhydroxy amino-carba sugar **43** in only four steps from the tropylium salt.

Conclusion

We have described our studies on the relatively unexplored chemistry of silylcycloheptatrienes. We showed that these readily available compounds largely react through their norcaradiene form in cycloaddition reactions with acylnitroso reagents, activated aldehydes and ketones, and triazolinedione. During these studies, we observed an unprecedented domino process involving four successive transformations, including an electrocyclic process, two hetero-Diels–Alder reactions, and one cationic cyclopropane ring opening. These cascades offer access to difunctionalized dienes that can also be obtained in an enantioenriched form and serve as useful intermediates for the synthesis of complex polycyclic systems and amino-carbasugar analogues. Mechanistic proposals have also been included that rationalize our observations. For instance, reactions between silylcycloheptatrienes and Lewis acids lead to different outcomes, depending on the nature of the Lewis acids. Whereas mild acids such as $Cu(OTf)_2$ or $Zn(OTf)_2$ likely catalyze hetero-Diels–Alder processes through the norcaradiene valence isomer, stronger $SnCl_4$ seems to favor cationic processes but also reactions through the cycloheptatriene form, providing mixture of products.

Experimental Section

Compound 16: *Method A*: 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (98 mg, 0.56 mmol, 1 equiv) and $Cu(OTf)_2$ (20.25 mg, 0.056 mmol, 0.1 equiv) were dissolved in CH_2Cl_2 (5 mL). The mixture was stirred at RT for 10 min, then **4b** (100 mg, 0.56 mmol, 1 equiv) was added. The mixture was stirred for 20 h at RT, then the solvent was removed under vacuum to provide a crude solid residue that was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 80:20 to 70:30), affording **16** (110 mg, 70%).

Method B: In a Schlenk apparatus were dissolved **15** (100 mg, 0.28 mmol, 1 equiv) and $Cu(OTf)_2$ (10 mg, 0.028 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (3 mL). The mixture was stirred for 20 h at RT, then the solvent was removed under vacuum to provide a crude solid residue that was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 80:20 to 70:30), affording **16** (36 mg, 46%). $R_f = 0.1$ (petroleum ether/EtOAc 80:20). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.74$ (br s, 1H), 7.53–7.31 (m, 5H), 6.15 (dd, $J = 5.4$, 9.6 Hz, 1H), 5.97 (dd, $J = 5.1$, 9.6 Hz, 1H), 5.86–5.70 (m, 2H), 5.65 (dd, $J = 4.5$, 9.3 Hz, 1H), 5.13 (dd, $J = 7.2$, 24.0 Hz, 2H), 4.92 (ddd, $J = 1.8$, 4.5, 6.0 Hz, 1H), 3.37–3.22 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 153.5$, 152.1, 136.6, 131.3, 129.2, 129.19, 128.7, 128.3, 125.6, 123.3, 121.5, 117.6, 54.8, 43.0 ppm; IR (film, NaCl): $\tilde{\nu} = 3443$, 1710, 1411, 1261, 1072, 736 cm^{-1}; MS (ESI): *m*/*z* (%): 585 (10) $[2M+Na]^+$, 304 (82) $[M+Na]^+$, 282 (45) $[M+H]^+$, 178 (100) [(4-phenyl-1,2,4-triazolidine-3,5-dione)+H]; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}N_3O_2Na$: 304.1056 $[M+Na]^+$; found: 304.1050.

Compound 22: To a flame-dried Schlenk tube were added $Cu(OTf)_2$ (40.5 mg, 0.122 mmol, 0.1 equiv) and Box(*t*Bu) (Aldrich 406147–250MG; 36.3 mg, 0.123 mmol, 0.11 equiv). The mixture was dried under vacuum for 1–2 h, then freshly distilled anhydrous CH_2Cl_2 (3 mL) was added and

the solution was stirred for 14 h. Fresh ethyl glyoxylate solution (50% in toluene, 344 mg, 1.68 mmol, 1.5 equiv) and triene **4b** (200 mg, 1.12 mmol, 1 equiv) were added. After stirring for the required reaction time (48 h), the reaction mixture was concentrated in vacuo and the crude product was directly purified by flash column chromatography (SiO_2; petroleum ether/EtOAc, 92:8), to afford (−)-**21** (140 mg, 60%) and **22** (12 mg, 5%). (−)-**21** compound *ee* was measured by chiral HPLC by using a Chiralpak-AD-H column [Hexanes/*i*PrOH, 95:5; 0.5 mL min^{-1}; 254 nm; 22°C; $t_R \approx 7.3$ (ent-1), 9.3 min (ent-2)].

Compound (−)-21: $R_f = 0.47$ (petroleum ether/EtOAc, 90:10); $[\alpha]_D^{26} = -122$ (*c* 0.8,$CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.08$–5.70 (m, 3H), 5.62 (dd, $J = 4.8$, 14.1 Hz, 1H), 5.42 (dd, $J = 4.8$, 14.1 Hz, 1H), 5.25–5.05 (m, 2H), 4.34–4.13 (m, 3H), 3.35–3.14 (m, 1H), 2.83–2.63 (m, 2H), 1.28 ppm (t, $J = 10.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 174.6$, 139.8, 129.7, 126.6, 123.13, 123.12, 116.6, 71.7, 61.9, 43.4, 40.7, 14.3 ppm; IR (film, NaCl): $\tilde{\nu} = 3489$, 1729, 1634, 1368, 1219, 1117, 1027, 735, 701 cm^{-1}; MS (ESI): *m*/*z* (%): 231 (100) $[M+Na]^+$; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{16}O_3Na$: 231.0991 $[M+Na]^+$; found: 231.0992.

Compound 22: $R_f = 0.45$ (petroleum ether/EtOAc, 90:10); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.58$–6.40 (m, 2H), 6.21–6.10 (m, 1H), 6.05–5.97 (m, 1H), 5.44–5.29 (m, 1H), 4.40–4.27 (m, 1H), 4.25–4.09 (m, 2H), 2.88–2.66 (m, 1H), 2.59 (dd, $J = 7.2$, 13.5 Hz, 1H), 2.33 (d, $J = 6.9$ Hz, 1H), 2.30–2.09 (m, 1H), 1.27 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 174.2$, 138.4, 130.2, 130.1, 126.7, 124.8, 120.8, 70.2, 61.7, 42.9, 32.5, 14.2 ppm. IR (film, NaCl): $\tilde{\nu} = 3456$, 1727, 1452, 1204, 1096, 699 cm^{-1}; MS (ESI): *m*/*z* (%): 231 (100) $[M+Na]^+$; HRMS (ESI): *m*/*z* calcd for $C_{12}H_{16}O_3Na$: 231.0991 $[M+Na]^+$; found: 231.0991.

Compound 28: $Cu(OTf)_2$ (20.25 mg, 0.056 mmol, 0.1 equiv) and Box(Ph) **23a** (22.4 mg, 0.067 mmol, 0.12 equiv) were added to a dry Schlenk apparatus. The mixture was dried under vacuum for 2 h, then freshly distilled anhydrous diethyl ether (3 mL) was added and the solution was stirred for 4 h. Diethyl ketomalonate **27** (146.3 mg, 0.84 mmol, 1.5 equiv) and triene **4b** (100 mg, 0.56 mmol, 1 equiv) were added and the reaction mixture was stirred for 48 h, then filtered over a pad of silica and the solvent was concentrated in vacuo. The crude product was directly purified by flash column chromatography (SiO_2; petroleum ether/EtOAc, 93:7), to afford **28** as a yellow oil (128 mg, 82%). The enantiomeric excess was measured as above by chiral HPLC by using a Chiralpak AD-H column. $R_f = 0.25$ (petroleum ether/EtOAc, 90:10); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.08$–5.91 (m, 1H), 5.90–5.63 (m, 2H), 5.53 (dd, $J = 7.8$, 14.4 Hz, 1H), 5.43 (dd, $J = 7.5$, 14.1 Hz, 1H), 5.10–4.87 (m, 2H), 4.22 (q, $J = 10.8$ Hz, 2H), 4.19 (q, $J = 10.8$ Hz, 2H), 3.72 (s, 1H), 3.24 (dt, $J = 2.1$, 7.2 Hz, 1H), 3.06–2.89 (m, 1H), 1.24 ppm (t, $J = 10.8$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 169.6$, 169.4, 139.4, 128.5, 126.8, 122.0, 121.4, 114.5, 82.2, 62.7, 62.5, 42.7, 38.5, 14.02, 14.0 ppm; IR (film, NaCl): $\tilde{\nu} = 3473$, 1736, 1634, 1368, 1219, 1144, 1033, 704 cm^{-1}; MS (ESI): *m*/*z* (%): 303 (66) $[M+Na]^+$, 197 (100) $[M+Na\text{-}(CO_2Et)_2OH]$; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}O_5Na$: 303.1202 $[M+Na]^+$; found: 303.1209.

Compound 40: *N*-Methylmorpholine oxide (NMO) (95 mg, 0.815 mmol, 1 equiv) and OsO_4 (0.45 mL, 2.5 wt% in *t*BuOH, 3.5 mol%) were sequentially added to a solution of diene **13a** (300 mg, 0.815 mmol, 1 equiv) in a mixture of THF and *t*BuOH (1:1 v/v, 15 mL) and H_2O (1.5 mL). The reaction mixture was stirred for 12 h at 20°C, then Na_2SO_3 (618 mg, 4.89 mmol, 6 equiv) and H_2O (10 mL) were added at 0°C and stirring was continued for 0.5 hour at 20°C. EtOAc and saturated aqueous NaCl were then added and the mixture was decanted. The aqueous layer was extracted with EtOAc (5×), and the combined extracts were dried over $MgSO_4$, filtered, and the solvents were removed in vacuo. To a solution of the above crude diol (220 mg, 0.55 mmol, 1 equiv) and pyridine (108 mg, 1.375 mmol, 2.5 eq) in CH_2Cl_2 (7 mL) was added acetic anhydride (224 mg, 2.2 mmol, 4 equiv). The reaction mixture was stirred for 12 h at 20°C, then quenched by addition of a saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (3× 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvents were removed in vacuo. The crude reaction mixture was purified by flash chromatography (SiO_2; petroleum ether/EtOAc, 70:30) to provide **40** (175 mg, 50%) as a yellow oil. $R_f = 0.2$ (petroleum ether/EtOAc, 70:30); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 6.62$–6.17 (m, 2H), 5.06–4.83 (m, 1H), 4.37–4.24 (m, 4H), 4.18–3.91 (m, 1H), 2.09–1.90 (m, 10H), 1.49–1.20 ppm (m, 18H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 170.3$, 169.5, 168.2, 156.9, 152.9, 132.0, 129.4, 83.4, 82.3, 71.3, 71.2, 71.0, 63.4, 50.9, 56.0, 37.5, 28.1, 28.0, 20.7, 20.5, 18.1 ppm; IR (film, NaCl): $\tilde{\nu} = 3457$, 2963, 1798, 1746, 1708, 1370, 1259, 1091, 1029, 800 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{36}N_2O_{11}Na$: 551.2211 $[M+Na]^+$; found: 551.2229.

Compound 42: To a stirred solution of **40** (110 mg, 0.21 mmol, 1 equiv) in anhydrous THF (2 mL), under nitrogen, was added dropwise at −78°C a freshly prepared solution of SmI_2 (22 mL of a 0.1 M solution in THF, prepared from I_2 and Sm in THF). After TLC analysis indicated completion of the reaction, the reaction mixture was diluted with EtOAc (36 mL) then quenched with a saturated solution of $Na_2S_2O_3$ (20 mL). The aqueous layer was extracted with EtOAc (5×). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvents were removed under vacuum to provide the crude hydroxycarbamate. NMO (20 mg, 0.17 mmol, 1 equiv) and OsO_4 (0.15 mL, 2.5 wt% in *t*BuOH) were sequentially added to a solution of the crude hydroxycarbamate (100 mg, 0.17 mmol, 1 equiv) in a mixture of THF and *t*BuOH (1:1 v/v, 6 mL) and H_2O (1 mL). The reaction mixture was stirred for 12 h at 20°C, then Na_2SO_3 (257 mg, 2.04 mmol) and H_2O (8 mL) were added at 0°C and stirring was continued for 0.5 h at 20°C. EtOAc and saturated aqueous NaCl were then added and the mixture was decanted. The aqueous layer was extracted with EtOAc (5×), and the combined extracts were dried over $MgSO_4$, filtered and the solvents were removed under vacuum. To a solution of the above crude triol (100 mg, 0.16 mmol, 1 equiv) and pyridine (89 mg, 1.12 mmol, 7 equiv) in CH_2Cl_2 (5 mL) was added acetic anhydride (114 mg, 1.12 mmol, 7 equiv). The reaction mixture was stirred for 12 h at 20°C, then quenched by the addition of a saturated ammonium chloride solution. The aqueous layer was extracted with diethyl ether (3×10 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvents were removed in vacuo. The crude reaction mixture was purified by flash chromatography (SiO_2; petroleum ether/EtOAc, 70:30) to afford the desired pentacetate **42** (76 mg, 53%) as a white solid that was recrystallized from EtOAc. $R_f = 0.2$ (petroleum ether/EtOAc, 70:30); M.p. 202–204°C (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 5.66$–5.53 (m, 1H), 5.46–5.16 (m, 3H), 4.80–4. 58 (m, 1H), 4.35–4.21 (m, 1H), 4.12–3.84 (m, 2H), 2.42–2.23 (m, 1H), 2.23–1.92 (m, 18H), 1.43 (s, 9H), 1.37 ppm (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 170.5$, 169.8, 169.4, 169.0, 167.8, 155.0, 154.1, 83.3, 80.8, 70.0, 69.3, 68.5, 67.9, 63.3, 55.0, 49.5, 36.6, 28.3, 27.9, 21.3, 21.0, 20.8, 20.74, 20.67, 18.2 ppm. IR (solid, KBr): $\tilde{\nu} = 3235$, 1744, 1702, 1693, 1368, 1223, 1165, 1096, 908 cm^{-1}; MS (ESI): *m*/*z* (%): 713 (11) $[M+Na]^+$, 657 (40) $[M+Na\text{-}(C_4H_8)]^+$, 613 (55) $[M+Na\text{-Boc}]^+$, 557 (100) $[M+Na\text{-}(C_4H_8)\text{-Boc}]^+$; HRMS (ESI): *m*/*z* calcd for $C_{30}H_{46}N_2O_{16}Na$: 713.2739 $[M+Na]^+$; found: 713.2741.

X-ray crystallography: CCDC-875114 (**15**), CCDC-875115 (**39a**), and CCDC-875113 (**42**), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.uc.uk/data_request/cif.

Acknowledgements

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Domino Reactions

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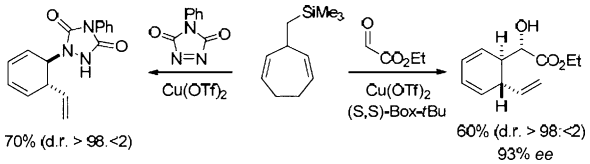
Development of Domino Processes by Using 7-Silylcycloheptatrienes and Its Analogues



Follow the path: 7-Silylmethylcycloheptatriene reacts either under thermal conditions or under Lewis acid catalysis through its norcaradiene valence isomer with various dienophiles, including acylnitroso reagents and activated aldehydes and ketones, to provide useful functionalized cyclohexa-1,3-dienes with high levels of stereocontrol (see scheme). ■■text shortened to fit, ok?■■

