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Synthetic Methods

Highly Functionalized and Potent Antiviral Cyclopentane Derivatives Formed by a Tandem Process Consisting of Organometallic, Transition-Metal-Catalyzed, and Radical Reaction Steps

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Abstract: A simple modular tandem approach to multiply substituted cyclopentane derivatives is reported, which succeeds by joining organometallic addition, conjugate addition, radical cyclization, and oxygenation steps. The key steps enabling this tandem process are the thus far rarely used isomerization of allylic alkoxides to enolates and single-electron transfer to merge the organometallic step with the radical and oxygenation chemistry. This controlled lineup of multiple electronically contrasting reactive intermediates provides versatile access to highly functionalized cyclopentane derivatives from very simple and readily available commodity precursors. The antiviral activity of the synthesized compounds was screened and a number of compounds showed potent activity against hepatitis C and dengue viruses.

Introduction

Functionalized cyclopentane derivatives are frequently occurring subunits of biologically active complex natural products and belong to the basic core structures of drug leads (Figure 1). Selected examples are the mulinane diterpenoids **A**,[1a] carijodienone **B**,[1b] dendroside F **C**,[1c] and hydrindane hedgehog signaling inhibitors **D**.[1d] A common feature is that they are part of complex ring systems, thus making synthetic approaches tedious multistep endeavors.[2]

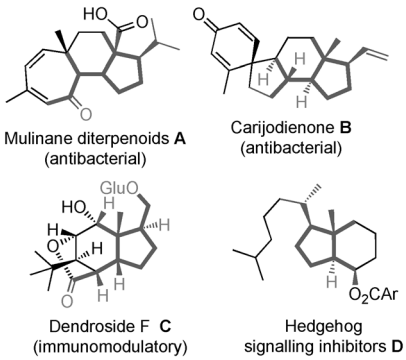

Figure 1. Selected biologically active natural products and drug leads featuring functionalized cyclopentane ring systems.

The complexity and diversity of such structures, which are important in biology, medicinal chemistry, and material sciences, leads to a strong demand for developing new synthetic methods for their synthesis. An attractive strategy to meet this challenge is the design of efficient one-pot reactions (domino, tandem, cascade reactions,[3] and multicomponent syntheses[4] are often synonymously used). They proceed with better time and resource efficiency than classical stepwise synthetic approaches and require less auxiliary materials for workup and purification of the target molecules.

However, several reaction types, such as nucleophilic additions of organometallic reagents **I** to carbonyl compounds **II**, although well developed, cannot be easily incorporated into one-pot, multistep processes, except for reaction of the resulting alkoxides **III** with electrophiles at oxygen giving **IV**

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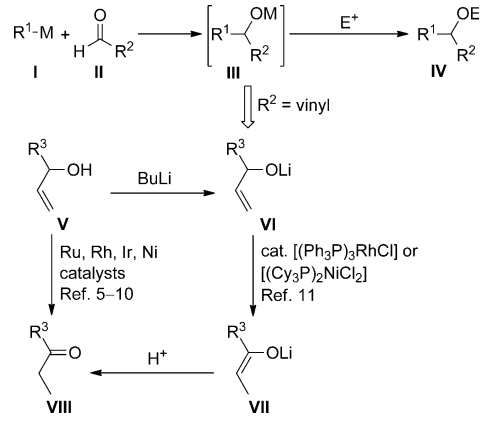
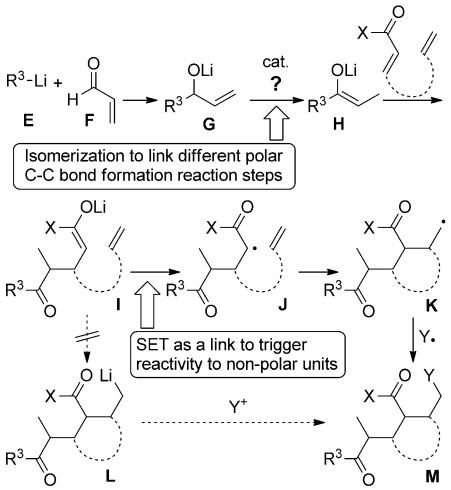


Scheme 1. Isomerization as a potential link to join nucleophilic addition with enolate chemistry.



Scheme 2. The strategy to couple the reactivity of electronically diverse intermediates mediated by isomerization and single-electron transfer. EWG = electron-withdrawing group.

(Scheme 1). From a strategic point of view, it would be attractive to transform **III** into a different reactive organometallic intermediate, from which further structural diversification through C–C bond formation can be achieved. Indeed, the transition-metal-catalyzed isomerization of neutral allylic alcohols **V** to ketones **VIII** is known.[5] It has also been extended to sequences with subsequent enzymatic reductions,[6] Heck reactions,[7] aldol additions,[5,8] Mannich reactions,[8b,9] fluorination,[10a,b] and chlorination of the resulting carbonyl compounds **VIII**.[10c] Almost nothing is known about the related isomerization of allylic alkoxides **VI**; Motherwell et al. reported the isomerization of allylic alkoxides **VI** to ketone enolates **VII** catalyzed by the Wilkinson complex[11a] or $[(Cy_3P)_2NiCl_2]$[11b] (Cy = cyclohexyl) and confirmed the formation of **VII** by coupling with an aldol addition.

This suggests that the isomerization of organometallic intermediates may provide an attractive link to line up multiple reactive intermediates with contrasting reactivities enabling tandem processes. Such a strategy has, however, not been developed apart from the above-mentioned aldol addition.[11a] Enolates **VII** are attractive intermediates for incorporation into one-pot sequences, as they may be applied in further polar C–C bond forming steps, such as Michael additions, during which another enolate intermediate is generated, which is positioned for additional reaction steps thus increasing their applicability.[12] In contrast, enolates **VII** are usually unable to undergo inter- or intramolecular additions to unactivated olefins.[13] Here, a switch by a single-electron oxidation to constitutionally identical free radicals, which undergo this type of reaction easily,[14] may provide a solution.

The validity of these hypotheses is documented herein. We report that the strategic application of redox isomerization and single-electron transfer (SET) is very useful to link the chemistry of reactive intermediates in one-pot processes, generating molecular complexity from simple and inexpensive precursors (Scheme 2). Main-group organometallic addition steps **E**+**F** and **H**→**I** are connected through transition-metal-catalyzed isomerization **G**→**H**. We provide a new and efficient catalytic system for this transformation. The resulting enolate **I** is demonstrated to switch reactivity by oxidative single electron transfer (**I**→**J**), providing the link to the radical cyclization manifold (**J**→**K**) to continue the sequence, because a potential anionic cyclization (**I**→**L**) does not proceed at all. The sequence is in most cases terminated at this stage by oxygenation (**K**→**M**), thus introducing further functionality (Y); however, a link into carbocation chemistry is also outlined in this paper. The products were screened with respect to their antiviral activity and some derivatives show potent activity. Thus, the approach provides new lead structures for antiviral compounds.

Results and Discussion

A focused optimization of the unknown, but crucial, nucleophilic addition/isomerization sequence was performed by addition of phenyllithium (**1a**) to crotonaldehyde (**2a**) followed by the addition of suitable selected ligands and catalysts (Table 1). The selection of the latter was based on an initial catalyst screening for the individual isomerization of **3a** (Supporting Information, Table S1). [Ru(*p*-cymene)Cl_2] (**Cat-1**; entries 1–6)[15] and the Wilkinson complex (**Cat-2**; entries 7–9)[11a] proved to be the most effective catalysts. It was found that $P(OMe)_3$ greatly accelerated the isomerization (entries 2–4, 8, and 9). Triphenylphosphine can be used similarly (entries 5 and 6), but its presence might later hamper purification of products. It was important that the ligands were present only in equimolar amounts with respect to the metal catalyst (entries 2 and 8 vs. 3 and 9). Larger quantities of the ligand decreased the activity of both catalytic systems. The reaction worked with similar results in refluxing dimethoxyethane (DME) and THF, thus demonstrating the stability of enolate **4a** under the reaction conditions. However, DME was preferred because of its lower tendency to act as a hydrogen donor in radical reactions. The formation of enolate **4a** as an intermediate was supported by α-

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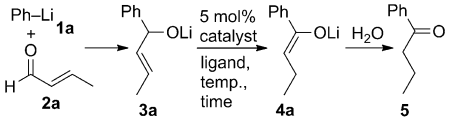
Table 1. Screening of conditions for the nucleophilic addition/isomerization sequence.



Entry	Catalyst	Ligand (equiv)[a]	T [°C]	Solvent	t [h]	**5** [%][b]
1	**Cat-1**	–	85	DME	1.0	91
2	**Cat-1**	$P(OMe)_3$ (1)	85	DME	0.5	99
3	**Cat-1**	$P(OMe)_3$ (2)	85	DME	1.0	85
4	**Cat-1**	$P(OMe)_3$ (2)	67	THF	2.0	99
5	**Cat-1**	PPh_3 (1)	85	DME	0.5	94
6	**Cat-1**	PPh_3 (2)	85	DME	0.5	84
7	**Cat-2**	–	85	DME	1.5	95
8	**Cat-2**	$P(OMe)_3$ (1)	85	DME	0.25	98
9	**Cat-2**	$P(OMe)_3$ (2)	85	DME	0.75	99
10	**Cat-3**	–	67	THF	5.0	10[c]

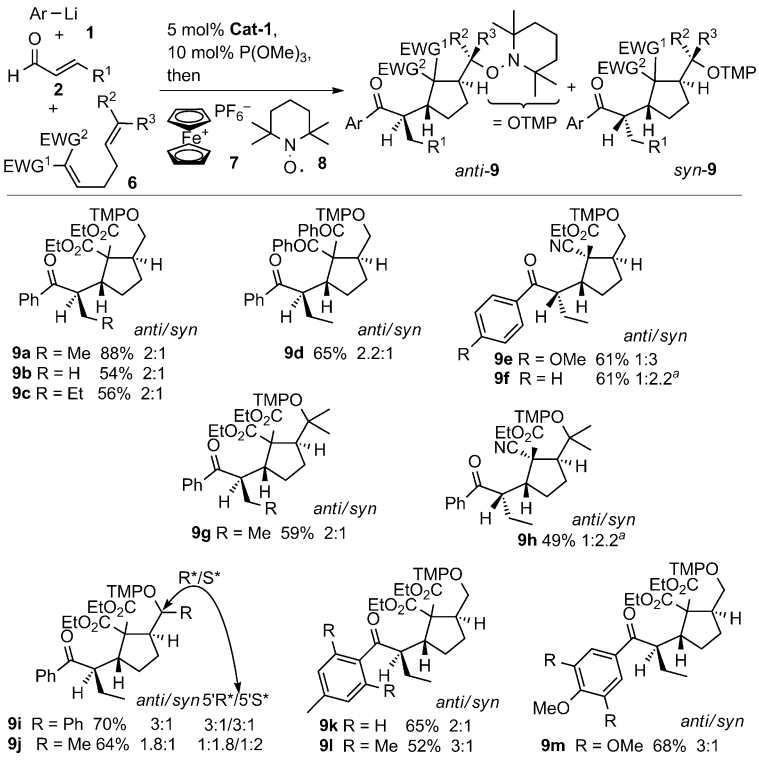
[a] Based on catalyst dimer. [b] Conversion determined by GC analysis using dodecane as internal standard. [c] 90% of 1-phenylcrotylalcohol was isolated. Catalyst decomposed during the addition of **1a**.

deuteration and formation of the corresponding silyl enol ether (for details see, the Supporting Information).

With optimal conditions for the isomerization of alkoxides to enolates established, the tandem sequence was elaborated; it consists of: 1) nucleophilic addition of several aryllithium reagents **1** to α,β-unsaturated aldehydes **2**, 2) isomerization catalyzed by **Cat-1**, 3) Michael addition of the resulting enolates to acceptors **6**, 4) SET oxidation to the corresponding radicals by selective SET oxidant ferrocenium hexafluorophosphate **7**,[16] 5) radical cyclizations to construct a five-membered ring, and finally 6) C–O bond formation by reaction with persistent radical TEMPO **8**[17] (Scheme 3). The substrate scope is broad and only two, often partly separable *anti* and *syn* diastereomers of cyclic oxygenated products **9a**–**m**, both having exclusive *trans* stereochemistry at the cyclopentane ring, were isolated. The alkyl chain of aldehydes **2** can be varied (**9a**–**c**). Remarkably, even the simplest member, acrolein (**2b**), which is often problematic in addition reactions, underwent the entire sequence, providing cyclopentane **9b** in 54% yield. Besides phenyllithium, a number of aryllithiums bearing alkyl or alkoxy groups in *para* and even *ortho* positions, flexibly generated by lithium–halogen exchange from the corresponding aryl bromides, can be applied successfully in the sequences (**9e**, **9k**–**m**). Ketone, ester, and nitrile functional groups are tolerated in Michael acceptors **6**, furnishing diversely substituted oxygenated 1,1-diacylcyclopentanes **9a**–**d**, **9g**, and **9i**–**m**. From prochiral alkylidene cyano acetates **6** ($EWG^1 = CO_2Et$, $EWG^2 = CN$) only two diastereomers of **9e**, **9f**, and **9h** were isolated; thus, three contiguous stereocenters at the ring were formed with high selectivity. Additionally, the *anti*/*syn* diastereoselectivity reverses with cyanoacetates. Substrates **6**, which have a prochiral olefin unit, can also be used in the sequence, providing cyclopentanes **9i** and **9j** with an additional chiral center in the substituent residing at the 5 position. Coupling of the cyclized radical with TEMPO (**8**) occurred with moderate diastereoselectivity.

The reaction sequences are not limited to the preparation of oxygenated compounds. A similar tandem reaction with silylated substrate **10** allows the preparation of vinylcyclopentane **11** in the absence of **8** (Scheme 4). The stability of β-silyl radicals to fragmentation[18] and the necessity to employ two equivalents of **7** indicates that two SET oxidation steps are involved in the sequence. The ability to access vinyl-substituted cyclopentanes **11** opens many pathways for further functionalization of this group.

The configuration of the minor diastereomer of compound **9a**, as well as that of the major diastereomers of **9e**, **9f**, **9i**, and **9j** was determined by X-ray crystallography (Figure 2).[19] It is shown that all compounds have an identical *trans* configuration at the ring and differ only at the exocyclic stereocenter. For cyclopentane-1,1-dicarboxylates **9a**, **9i**, and **9j** the *anti* diastereomer between the ring and the exocyclic stereocenter next to the carbonyl group is preferentially formed, whereas the *syn* diastereomer is preferred in cyano-substituted cyclopentanes **9e** and **9f**. The configuration of the other products was assigned on the basis of NOE investigations.



Scheme 3. Tandem addition/isomerization/Michael addition/radical cyclization/oxygenation reactions (only the major diastereomer is shown). [a] Two additional diastereomers were detected in trace amounts in the NMR spectra.

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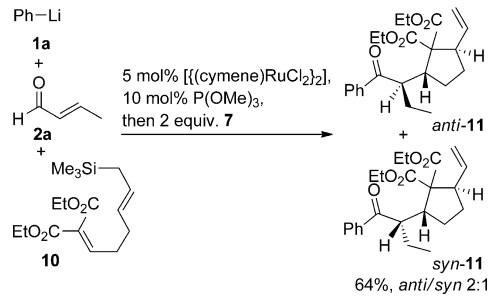


Scheme 4. Nucleophilic addition/isomerization/Michael addition/SET oxidation/radical cyclization/SET oxidation/desilylation sequence. Based on resonances in the ^{1}H NMR spectrum, traces of two other diastereomers may have formed.

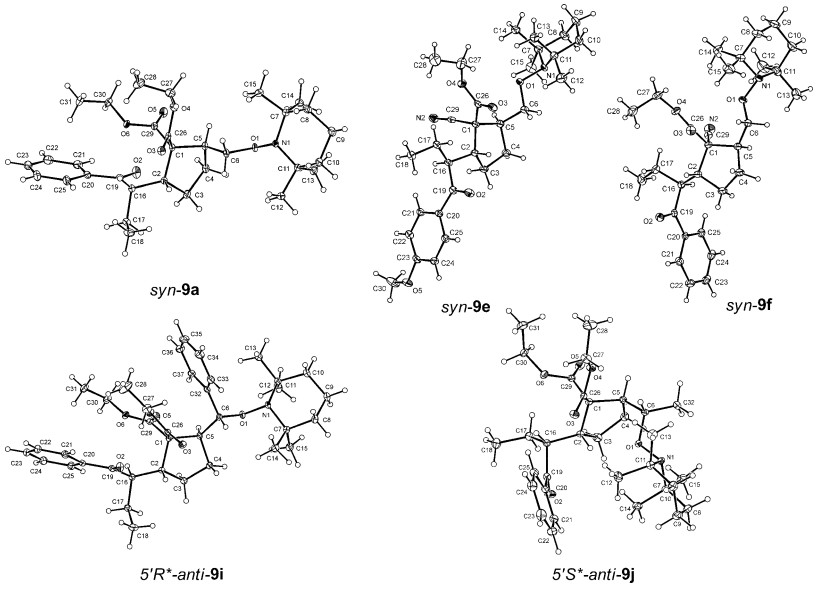
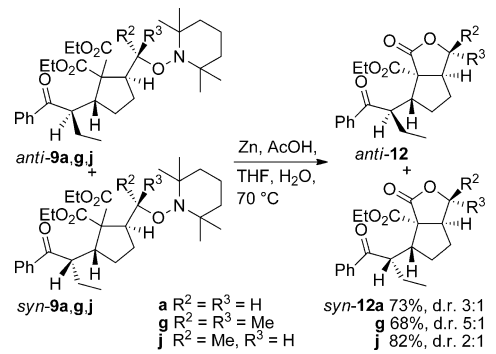


Figure 2. Structure determination of the minor diastereomer of **9a** and the major diastereomers of **9e**, **9f**, **9l**, and **9j** by X-ray crystallography. Displacement ellipsoids are drawn at the 30% probability level.

Oxygenated compounds **9** are protected alcohols. Their deprotection was achieved by treatment of **9a**, **9g**, and **9j** with zinc in the presence of acetic acid (Scheme 5). Lactonization to bicyclic compounds **12a**, **12g**, and **12j** was observed under the reaction conditions. This favorable result allows differentiation of the two carboxylic acid groups, thus providing the prospect for further selective manipulation of the two groups in target-oriented synthesis. Moreover, the configuration at the stereocenter bearing the aminoxy group in **9j** was determined in this way.

Compounds **9** were tested against different genotypes of the HCV virus in the 1A-, 1B-, and 2A replicon assays, and the dengue virus in vero cells (Table 2). The results show that compounds **9a**–**c**, which are unsubstituted at the aryl ring, show nanomolar to low micromolar activity against genotype 1 HCV and the dengue virus (entries 1–3). The anti-HCV acitivity against genotype 1 is relatively independent of the substitution pattern at the arene ring and the 1 and 5 positions (entries 3–8). However, larger substituents at the arene ring, the 5 position and the replacement of one ethyl ester unit by the cyano group lead to a large decrease in the activity against the dengue virus (entries 5–8). All other compounds, **9d**, **9e**, **9g**–**i**, and **9m**, were also tested, but were not active in both assays. Remarkably, all of the compounds tested, except for **9e**, were not cytotoxic to huh-7, vero, or hela cell lines up to 50 μM, the highest concentration tested. All compounds were subsequently tested in an MT-4 cell line, which is a rapidly growing T cell line, ideally suited for measuring the cytotoxic effects of small-molecule antivirals. In this more sensitive cell line, all of the compounds tested were >25 μM. Specifically, compound **9c** (entry 3) was 42 μM, leading to a selectivity index of about 100-fold for the genotype 1b replicon (MT4 CC_{50}/EC_{50} 1b replicon). Furthermore, compound **9c** was not active toward other RNA viruses, for example, RSV and hRV, thus demonstrating



Scheme 5. Reductive removal of the tetramethylpiperidinyl unit in **9a**, **9g**, and **9j**.

Table 2. Antiviral activity of compounds **9** against different HCV genotypes and the dengue virus.[a]

Entry	9	HCV Replicon 1B EC_{50} [μM]	HCV Replicon 1A EC_{50} [μM]	HCV Replicon 2A EC_{50} [μM]	DENV-2 EC_{50} [μM]
1	**a**	2.3	3.8	25.3	8.4
2	**b**	4.2	3.8	28.9	2.1
3[b]	**c**	0.4	1.2	36.3	4.8
4[c]	**c**	1.2	0.6	26.5	8.8
5	**f**	9.5	16.9	>50	>50
6	**j**	4.7	11.2	43.9	>50
7	**k**	3.2	5.4	41.9	>50
8	**l**	7.7	16.3	>50	>50

[a] Cytotoxicity (CC_{50}) values are >50 μM for all compounds except **9e** (35.9 μM). [b] Diastereomeric mixture. [c] Individual major diastereomer.

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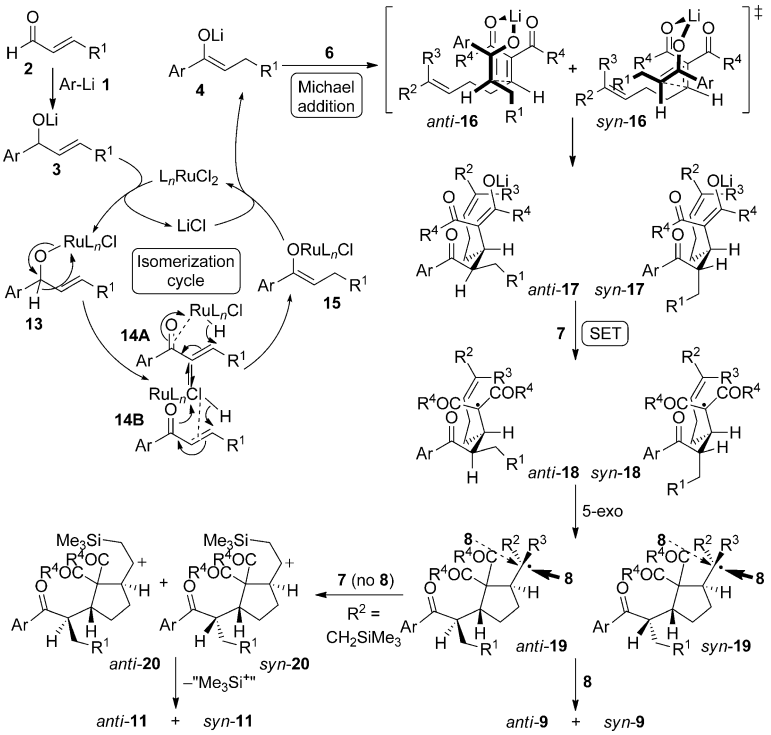
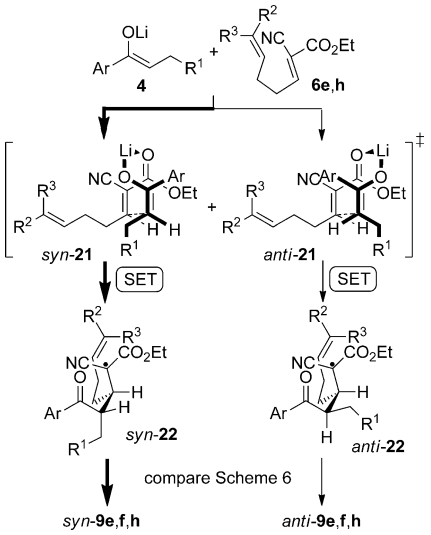


Scheme 6. Mechanistic and stereochemical rationale of the tandem sequences.

that the compound is not a broad-spectrum antiviral toward RNA viruses. The detailed mechanism of action for these compounds requires further studies.

The mechanistic course and the diastereoselectivity can be rationalized as follows (Scheme 6): Nucleophilic addition of arylllithium compounds **1** to unsaturated aldehydes **2** generates allylic alkoxides **3**, which enter the ruthenium-catalyzed isomerization cycle[5–10] by a transmetalation to the ruthenium alkoxides **13**. Hydride transfer to ruthenium leads to complexes **14A** or **14B** with the coordinated enone unit. Conjugate addition of the hydride ligand furnishes ruthenium enolates **15**,[20] which transmetalate with lithium chloride, thus liberating lithium enolates **4** and regenerating the ruthenium catalyst. The enolates **4** undergo a Michael addition to unsaturated carbonyl compounds **6**. The results indicate that the additions of enolates **4** to malonate or dibenzoylmethane derivatives **6** (R^4 = OEt or Ph) proceed via chelated transition states *anti*- and *syn*-**16**,[12,21] in which the lithium atom of the enolates **4** coordinates the *Z*-oriented carbonyl group.[21] The orientation in transition state *anti*-**16** is more favorable than that in *syn*-**16**, however, from the moderate diastereoselectivity obtained, it can be concluded that the energetic difference between them is moderate in all cases. The resulting enolates *anti*- and *syn*-**17** are stabilized and thus unreactive to further organometallic reaction steps. However, the cyclization is triggered by single-electron-transfer oxidation with **7** to give radicals **18**. They undergo the subsequent radical cyclization with exclusive *trans* diastereoselectivity, which can be rationalized on the basis of a Beckwith–Houk transition state, which places the substituents and the alkene unit in pseudoequatorial positions of a chair-like arrangement.[22] An alternative boat transition state seems to be highly unfavored. Further diversification is possible from cyclic radicals **19**. Radical coupling with TEMPO **8** provides the products **9**. This coupling proceeds with prochiral radicals **19** ($R^2 \neq R^3$) with a reasonable level of diastereoselectivity. TEMPO **8** approaches the radical preferentially from the unhindered face opposite to the acyl groups. The conformation of the radical center is determined by A-strain, which forces the larger substituent R^2 to the α face. Importantly, more readily oxidizable radicals **19**, such as those bearing trimethylsilyl groups,[23] are transformed by an excess of **7** into carbocations **20**, which stabilize to vinylcyclopentanes **11** by desilylation. This result clearly demonstrates the potential to extend these sequences by additional carbocationic reaction steps.

The *Z* coordination mode of enolate **4** is not possible in cyano acetate derivatives **6e** and **6h** (Scheme 7). They can only coordinate through the *E* carbonyl group in transition state **21**, thus leading to the preferred formation of the *syn* Michael adduct enolates, which are subject to SET oxidation to generate radicals *syn*- and *anti*-**22e**, **22f**, and **22h**. The subsequent radical cyclization of *syn*- and *anti*-**22**, proceeds with high diastereoselectivity via a transition state in which the smaller cyano substituent is located in a pseudoaxial orientation (see the Supporting Information, Scheme S2).



Scheme 7. Reversed diastereoselectivity in sequences involving cyanoacetates.

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Conclusion

We report here an unprecedented tandem process consisting of main-group organometallic, transition-metal-catalyzed, and radical reaction steps. The controlled use of two- and single-electron-transfer steps enables the selective manipulation of a wide variety of reactive intermediates in the sequence, which provides easy access to complex cyclopentanes from inexpensive commodity chemicals. Overall, nine to ten elementary steps were lined up in sequence, during which one C–O and three C–C bonds were formed, and a C–H bond was translocated. The average efficiency for each of these elementary steps amounts to 92% for product **9h**, which was isolated with the lowest yield of 49%, but reaches or exceeds 95% for most other products **9**. Reactivity incompatibilities, such as the non-proceeding cyclization of the organometallic enolate, were overcome by switching to the constitutionally identical, but considerably more reactive, radical intermediate. Similarly, the facile SET oxidation of cyclic radicals to the corresponding carbocations during the formation of vinylcyclopentane **11** is a promising extension. Several individual parts of the sequences, such as the optimized catalytic conditions for isomerization, are useful for other applications. The reported redox and intermediate diversity promises to significantly increase the flexibility of synthetic planning toward more efficient target-oriented syntheses of natural products, drug leads, and materials. An antiviral screen revealed the promising activity of some derivatives against the hepatitis C genotype 1 and dengue viruses, with no significant toxicity, thus providing a new and easily accessible lead for further investigation.

Experimental Section

General procedure using lithium–halogen exchange

*t*BuLi (1.53 mL, 2.6 mmol, 1.7 M in pentane) was added to a stirred solution of the aryl halide (1.3 mmol) in DME (8 mL) at −78 °C under an argon atmosphere. After 35 min, the α,β-unsaturated aldehyde **2** (1.3 mmol) was added at once. After stirring at the same temperature for 15 min, (*p*-cymene)ruthenium dichloride dimer (39.7 mg, 0.065 mmol, 5 mol%) was added. The flask was removed from the cooling bath, $P(OMe)_3$ (0.016 mL, 0.13 mmol, 10 mol%) was added dropwise and the mixture was stirred at room temperature for 5 min. The homogeneous solution was heated at a temperature of 86 °C in an oil bath until conversion of the allylic alkoxide **3** to ketone enolate **4** was complete based on TLC or GC analysis, typically 30–45 min. The reaction mixture was cooled to −45 °C and the diene **6** (1 mmol) in dry DME (2 mL) was added. The reaction mixture was stirred at the same temperature until complete (3–4 h). TEMPO **8** (47 mg, 0.3 mmol) was added followed by a thoroughly homogenized mixture of TEMPO **8** (110 mg, 0.7 mmol) and ferrocenium hexafluorophosphate **7** (331 mg, 1 mmol) in small portions with vigorous stirring. Additional **7** (ca. 165 mg, 0.5 mmol) was added until the reaction mixture became blue-green. Stirring was continued for 20 min. The reaction was quenched by a few drops of water and then filtered through a pad of silica gel, which was washed thoroughly with diethyl ether. The filtrate was evaporated under vacuum, the crude product was preadsorbed on silica gel, and then purified by flash column chromatography (gradient of hexanes/EtOAc, 100:1 to 1:1). Ferrocene eluted first, followed by some phenones **5**, TEMPO **8**, and cyclization products **9**, respectively.

Vinylcyclopentanedicarboxylate (11)

Phenyllithium **1a** (0.72 mL, 1.3 mmol, 1.8 M in dibutyl ether) was added dropwise to α,β-unsaturated aldehyde **2a** (1.3 mmol) in DME (8 mL) at −5 °C under an argon atmosphere. After stirring for 15 min, (*p*-cymene)ruthenium dichloride dimer (39.7 mg, 0.065 mmol, 5 mol%) was added. The flask was removed from the cooling bath, $P(OMe)_3$ (0.016 mL, 0.13 mmol, 10 mol%) was added dropwise, and the mixture was stirred at room temperature for 5–10 min. The homogeneous solution was heated at a temperature of 86 °C in an oil bath until conversion of the allylic alkoxide **3a** to ketone enolate **4a** was complete based on TLC or GC analysis, typically 30–45 min. The reaction mixture was cooled to −45 °C and the diene **10** (312.5 mg, 1 mmol) in dry DME (2 mL) was added. The reaction mixture was stirred at the same temperature until completion (3–4 h). Ferrocenium hexafluorophosphate **7** (662 mg, 2 mmol) was added in one portion. Additional ferrocenium hexafluorophosphate (ca. 165 mg, 0.5 mmol) was added until the reaction mixture became blue-green. Stirring was continued for 20 min. The reaction was quenched by a few drops of water and then filtered through a pad of silica gel, which was washed thoroughly with diethyl ether. The filtrate was evaporated under vacuum, the crude product was preadsorbed on silica gel, and then purified by flash column chromatography (gradient of hexanes/EtOAc, 100:1 to 2:1). Ferrocene eluted first followed by some phenone **5**, and the cyclized product **11**, respectively.

Typical procedure for deprotection of compounds 9a, 9g, and 9j

A 3:1 diastereomeric mixture of **9a** (100 mg, 0.188 mmol) was dispersed in a mixture of acetic acid (1.1 mL) and water (0.4 mL). THF was added dropwise until a homogeneous solution was formed (1 mL). Zinc dust (555 mg, 8.46 mmol) was added with vigorous stirring and the reaction mixture was heated at 80 °C for 1 h. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and filtered. The filtrate was neutralized with saturated K_2CO_3 solution to a pH of about nine. The organic layer was separated, washed twice with water, dried over Na_2SO_4, and evaporated to give the crude product, which was purified by flash chromatography (gradient of hexanes/EtOAc, 100:1 to 2:1).

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Keywords: antiviral activity · cyclopentanes · isomerization · organic synthesis · radicals

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[20] Alternative mechanisms by hydrometalation or migratory insertion of the ruthenium hydride unit in **14** followed by reductive elimination may be possible. See refs [5–10]. For a very recent experimental and computational study of the mechanistic isomerization alternatives in a ruthenium-catalyzed isomerization of allylic alcohols, see ref. [5e].

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