

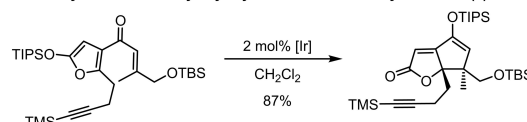
A Nazarov-Ene Tandem Reaction for the Stereoselective Construction of Spiro Compounds

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In memory of Klaus Hafner (1927–2021)

Abstract: The different reactivity of trienones under Lewis and Brønsted acids catalysis was investigated, resulting in distinct cyclization products and carbon backbones that originated either from a conjugate Prins cyclization or an interrupted Nazarov cyclization. In particular, an unprecedented Nazarov cyclization tandem reaction is presented, terminating the oxyallyl cation by an ene-type reaction, and leading stereoselectively to bicyclic spiro compounds. The terminal olefin of this motif represents a useful handle for further functionalization, making it a strategic intermediate in total syntheses. The tandem Nazarov/ene cyclization was shown to be preferred over a Nazarov/[3 + 2] tandem reaction for all our substrates, independent of chain length. Deuteration studies further support the mechanistic hypothesis of the terminating ene reaction.

The Nazarov reaction is an acid-catalyzed cyclization of dienones involving a 4π -electrocyclization and leading to cyclopentenones. Although the first Nazarov cyclization dates back to 1941, it is constantly refined to extend its potential for the construction of 5-membered rings in the context of total synthesis. Recent examples in which such improvements have been utilized are the total syntheses of (\pm)-merrillactone A,^[1] (\pm)-rocaglamide^[2] and (–)-calyphylline N^[3] (Scheme 1). Moreover, disrotatory cyclizations of photochemical excited state

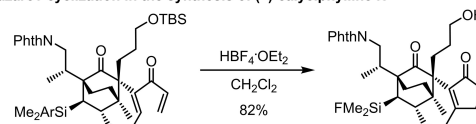
Nazarov cyclization of a silyloxyfuryl enone in the total synthesis of (\pm)-merrillactone A^[1]



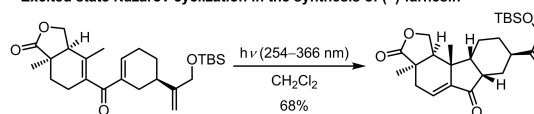
Nazarov cyclization initiated by epoxide opening in the synthesis of (\pm)-rocaglamide^[2]



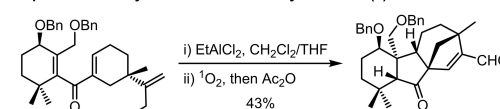
Nazarov cyclization in the synthesis of (–)-calyphylline N^[3]



Excited state Nazarov cyclization in the synthesis of (–)-farnesin^[4]



Interrupted Nazarov cyclization in the total synthesis of (–)-oridonin^[10]



Scheme 1. Nazarov key steps in the total syntheses of (\pm)-merrillactone A,^[1] (\pm)-rocaglamide,^[2] (–)-calyphylline N,^[3] (–)-farnesin and (–)-oridonin.^[10] Bn = benzyl, *m*CPBA = *m*-chloroperoxybenzoic acid, DMF = *N,N*-dimethylformamide, Phth = phthaloyl, PMB = *p*-methoxybenzyl, PMP = *p*-methoxyphenyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

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Nazarov reactions open new opportunities for the selective synthesis of complex natural products as exemplified by the total synthesis of (–)-farnesin (Scheme 1).^[4]

In the late 90s, West and co-workers reported on interrupted Nazarov reactions,^[5] during which the oxyallyl cations produced in the electrocyclization step, is the comma correct? are trapped either by a nucleophile in a S_N1 -like process, a [3 + 2] reaction,^[6] a [4 + 3] cycloaddition,^[7] or through a Wagner–Meerwein rearrangement.^[8] By using interrupted Nazarov reactions, and taking advantage of the pericyclic nature of this process, it is possible to control up to four contiguous stereocenters.^[9] The recently published synthesis of (–)-oridonin

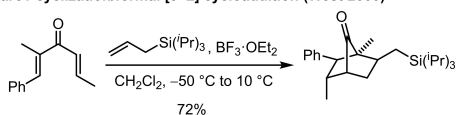
(Scheme 1) is such an example in which the interrupted Nazarov cyclization unfolded its full potential.^[10]

Our interest in the interrupted Nazarov cyclization stemmed from ongoing synthetic endeavors on polycyclic and bridged natural products. West and co-workers investigated both the formal [3 + 2] cycloaddition of allyl silanes to Nazarov-derived oxyallyl cations,^[6] and the simultaneous construction of tricyclic frameworks in intramolecular Nazarov cyclization/[4 + 3] cycloaddition tandem sequences (Scheme 2).^[7a]

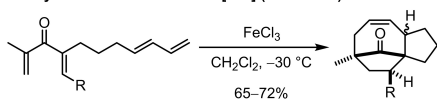
In this context, we considered the synthesis of illisimonin A (1) with its unprecedented tricyclo[5.2.1.0^{1,6}]decane backbone^[11] as the litmus test for the interrupted Nazarov cyclization. The above mentioned skeleton could be conveniently disconnected through a Nazarov cyclization/formal [3 + 2] cycloaddition tandem reaction, leading to trienone 2 (Scheme 3).

We herein report our investigations on the cyclization behavior of trienones like 2, giving an insight to the Lewis acid dependent competition between a conjugate Prins cyclization and the Nazarov cyclization. We report the discovery of an unprecedented Nazarov/ene cyclization tandem reaction for the stereoselective construction of spirocyclic molecules, which extends the recently published ene-type reactions of oxyallyl cations with tethered olefins by the Saicic group (Scheme 2).^[12]

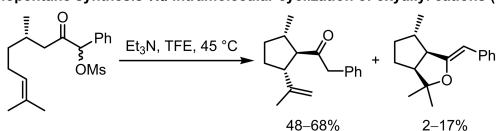
Nazarov cyclization/formal [3+2] cycloaddition (West 2000)^[6]



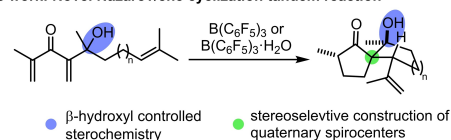
Nazarov cyclization/intramolecular [4+3] (West 1999)^[7a]



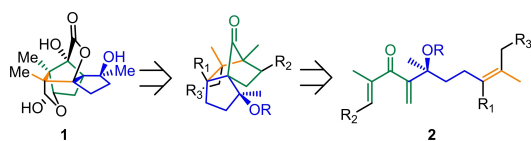
Cyclopentane synthesis via intramolecular cyclization of oxyallyl cations (Saicic 2019)^[12]



This work: Novel Nazarov/ene cyclization tandem reaction



Scheme 2. Supporting literature to the retrosynthetic approach towards illisimonin A (1), and the novel interrupted Nazarov cyclization. Ms = methanesulfonyl, TFE = 2,2,2-Trifluoroethanol.



Scheme 3. Interrupted Nazarov cyclization approach to the core of illisimonin A (1).

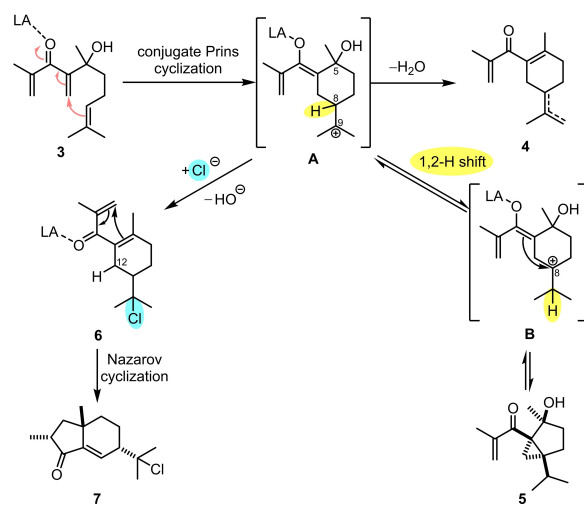
In order to explore the general reaction conditions, we started our investigations with simplified 3, reduced to the essential functional groups that the envisioned cyclization required (Scheme 3).

The initial Lewis acid screening showed that a strong competitor of the Nazarov cyclization was a reaction pathway that initiated through conjugate addition of the side chain double bond to the central enone double bond (Table 1; marked carbons 8 and 12).^[13] This resulted, depending on the employed Lewis acid, in the formation of products 4 to 7. We later refer to these products as derived from the Michael-Prins pathway.

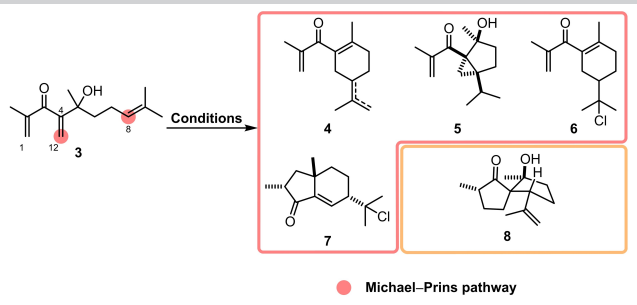
Monocyclic trienone 4 was observed as main product with Lewis or Brønsted acids that required elevated temperatures to drive the reaction to completion, and were lacking nucleophilic counterions (Table 1, entries 1–4). We rationalized its formation by formal water loss from intermediate A (Scheme 4).

In contrast, trapping of A occurred when the metal chlorides FeCl₃, TiCl₄ or SnCl₄ (Table 1, entries 6–9) were used. Interception of the cation by chloride, and hydroxyl elimination afforded cross-conjugated ketone 6, which was observed as the main product with SnCl₄ (Table 1, entry 9; Scheme 4). Interestingly, the reaction appeared to stop at this stage for the SnCl₄-mediated cyclization, while 4th period metal chlorides were able to initiate a Nazarov cyclization of 6 to give bicyclic ketone 7 (Table 1, entries 6–8; Scheme 4).

In case of TiCl₄, we additionally found that cyclopropane 5 was formed alongside 7, if the reaction was performed at –78 °C (Table 1, entry 6). Its formation was rationalized through an initial 1,2-hydride shift of intermediate A, that translocated the carbocation to position 8 – in reach of the enol moiety for ring closure to the cyclopropane (Scheme 4). Slightly higher reaction temperatures shifted the product distribution towards 7, leaving no detectable amounts of 5 (Table 1, entry 8). We reasoned that both products were formed *via* two competing reaction pathways (Scheme 4), with the cyclopropane formation being reversible.^[14] Acidic fragmentation of the cyclopropane at



Scheme 4. Proposed reaction pathways for the formation of products 4 to 7. LA=Lewis acid.

Table 1. Initial Lewis acid screening for cyclization of **3** and optimization towards **8**.


Entry	Lewis acid	Conditions	Product (Yield ^[a,b])
1	AgOTf (1.1 equiv.)	CH ₂ Cl ₂ , r.t., 3 h	4 (64%)
2	Bu ₂ OTf (1.0 equiv.)	Et ₂ O, −78 °C, 2 h; then r.t. 4 min	4 (45%)
3	TMSOTf (2.0 equiv.)	MeLi (1.0 equiv.), Et ₂ O, −78 °C; then TMSOTf, −78 °C to r.t., 6 h	4 (40%)
4	(PhO) ₂ P(O)NHTf (1.0 equiv.)	MeCN, 4 Å MS, −20 °C to r.t., 41 h	4 (46%)
5	BF ₃ ·Et ₂ O (1.0 equiv.)	CH ₂ Cl ₂ , −78 °C, 7.5 h	5 (51%)
6	TiCl ₄ (2.1 equiv.)	CH ₂ Cl ₂ , −78 °C, 1.5 h	5 (11%), 7 (11%) ^[c]
7	FeCl ₃ (1.0 equiv.)	CH ₂ Cl ₂ , −78 °C (25 min) to 0 °C (3.5 min) to r.t. (o/n)	7 (14%) ^[c]
8	TiCl ₄ (2.1 equiv.)	CH ₂ Cl ₂ , −50 °C, 1 h	7 (22%) ^[c]
9	SnCl ₄ (1.0 equiv.)	CH ₂ Cl ₂ , −78 °C to 0 °C	6 (43%) ^[c]
10	B(C ₆ F ₅) ₃ (20 mol%)	CH ₂ Cl ₂ , −84 °C to −50 °C to r.t., 24 h	4 (11%), 8 (11%)
11	B(C ₆ F ₅) ₃ (1.0 equiv.)	Et ₂ O, 0 °C, 45 min	4 (28%), 8 (16%)
12	B(C ₆ F ₅) ₃ ·H ₂ O (1.1 equiv.)	Et ₂ O, r.t., 1.5 h	8 (41%)
13	B(C ₆ F ₅) ₃ ·H ₂ O (2.5 mol%)	CH ₂ Cl ₂ , r.t., 20 h	8 (41%)
14	B(C ₆ F ₅) ₃ (2.5 mol%)	CH ₂ Cl ₂ , r.t., 40 h	8 (32%)
15	B(C ₆ F ₅) ₃ (5 mol%)	toluene, r.t., 36 h	8 (41%), (32%) ^[d]

[a] Isolated yield after column chromatography. [b] Yields refer to a scale of 50 mg to 70 mg (225 μmol to 315 μmol) of **3**. [c] Obtained as inseparable mixture with a constitutional isomer (see Supporting Information). [d] 25 mmol scale. MS=molecular sieve, o/n=overnight, r.t.=room temperature, Tf=trifluoromethanesulfonyl.

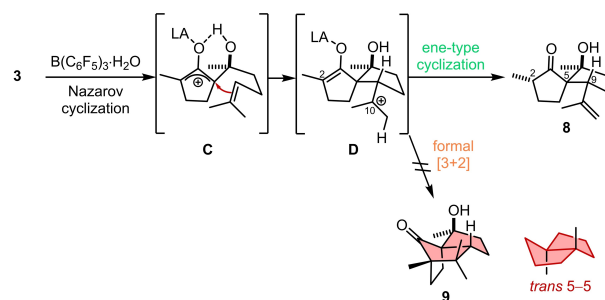
slightly elevated temperatures would regenerate intermediate **B**, which is likely to exist in equilibrium with **A**.^[15] Irreversible cation trapping and water elimination would drive the reaction towards bicyclic ketone **7**; **5** could be obtained in good yield through BF₃-mediated cyclization of **3** at −78 °C (Table 1, entry 5).

Confronted with the realization that the Michael-Prins pathway was the prevailing mode of reactivity for **3**, we were pleased to discover that spirocycle **8** – as product of an interrupted Nazarov cyclization – can be obtained if tris(pentafluorophenyl)borane (TPPB) is used. Inspired by the work of Oestreich and co-workers,^[16] we first examined the use of substoichiometric amounts of this Lewis acid in CH₂Cl₂, which afforded spirocycle **8** alongside Michael-Prins product **4** in low yield due to extensive decomposition (Table 1, entry 10). Stoichiometric use of Lewis acids in Et₂O, as a coordinating and potentially dampening solvent,^[17] reduced the extent of decomposition, but mainly improved the yield of undesired product **4** (Table 1, entry 11).

To our delight, the use of B(C₆F₅)₃·H₂O, which has been used as an efficient mediator of vinylogous Mukaiyama aldol reactions in our group,^[18] significantly increased the yield of **8** to 41% (Table 1, entry 12). For the stoichiometric conditions, the conduction of the reaction in Et₂O at room temperature was superior to all other examined solvents and reaction temperatures (see Supporting Information).

In contrast, we found that the observed interrupted Nazarov cyclization can be performed catalytically in non-coordinating solvents, with catalyst loadings reduced down to 2.5 mol% without compromised yield (Table 1, entry 13). We thereby found that the combinations of B(C₆F₅)₃·H₂O in CH₂Cl₂ and B(C₆F₅)₃ in toluene were equally efficient conditions for the cyclization (Table 1, entries 13 and 15).

Spiro compound **8** was obtained as a single diastereomer, with selective construction of the stereocenters at positions 5 and 9, and defined stereochemistry at position 2 (Scheme 5). We proposed that the stereoselectivity arises from hydrogen bonding between the precursor's β-hydroxyl group and



Scheme 5. First mechanistic hypothesis for the formation of spirocycle **8** from **3**. An ene reaction is favored over the envisioned [3+2] cyclization.

carbonyl group, which determines the side from which the olefin approaches the oxyallyl cation (C, Scheme 5).

Since the initially envisioned formal [3 + 2] cyclization to the hypothetical tricyclic ketone **9** did not occur, we assumed that cationic intermediate **D** preferably underwent elimination to afford **8** in an ene-like cyclization (Scheme 5).

As the group of West had mainly described the [3 + 2]-mode of interruption for allyl silanes,^[6] we contemplated if a silyl group in the precursor's side chain could stabilize a cationic intermediate **D**, and prolong its life time enough to allow the full cyclization to **9**.

Exposure of silylated precursor **10** to our stoichiometric cyclization conditions, however, gave mainly the undesired conjugate addition product **4** (Scheme 6), presumably due to the increased nucleophilicity of the allyl silane double bond.

In addition to **4**, traces of silylated spiro compound **11** were isolated. This observation posed a surprise, as the silyl group was not lost during the cyclization, as we would have expected for a stepwise mechanism with a distinct cationic intermediate **D** (Scheme 5).^[19] It instead appeared that the reaction proceeds with selective transposition of the side chain's double bond to the position of the former (*E*)-methyl group of the starting material. This proposal was further confirmed when we investigated the cyclization of trienone **12** (Scheme 6), in which the (*Z*)-methyl group had been furnished with a TBS protected alcohol. Exposure of **12** to our catalytic cyclization conditions provided functionalized spirocycle **13** with the (*Z*)-substituent

untouched during cyclization. A more detailed mechanistic discussion will be given in the text below.

It is thereby remarkable that the cyclization of functionalized substrate **12** proceeded as efficiently as the cyclization of its unfunctionalized congener **3** (Table 1, entry 15; Scheme 6, b). The example demonstrates that the observed interrupted Nazarov cyclization can tolerate functionality at the (*Z*)-substituent of the interrupting double bond, if the double bond's electronic properties are not strongly influenced.

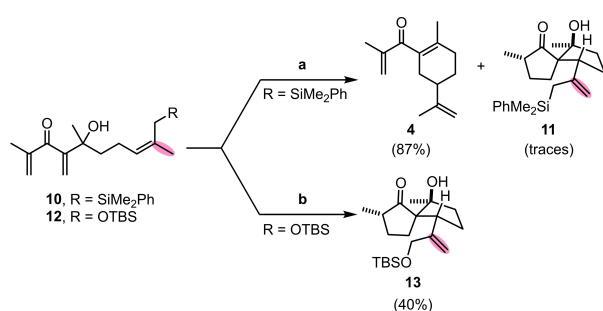
Unable to observe the desired [3 + 2] tricyclic, we reasoned that the three-atom tether that connects oxyallyl-cation and approaching double bond in **3** only offers limited conformational flexibility, and forces the double bond into an orientation that does not allow a formal [3 + 2] cycloaddition. For the full cyclization, the reacting centers (positions 2 and 10, **D**, Scheme 5) would have to move towards each other against the strain of the newly formed 5-membered ring, to form a *trans*-fused 5/5- ring system.^[20]

To see if a more flexible tether could affect the outcome of the reaction, we investigated the cyclization of **14**, with four carbon atoms separating the reaction partners.

Our condition screening showed, however, that spiro compound **15** – the homologue of Nazarov product **8** (Table 1) – was the preferred cyclization product under the examined conditions (see Supporting Information). Remarkably, exposure of **14** to catalytic amounts of $B(C_6F_5)_3$ afforded **15** in a good yield of 77% (Table 2, entry 1). Products of the Michael-Prins pathway could not be observed for **14**. We hypothesized that the 7-*endo-trig* cyclization that would initiate this process is slower than the 6-*endo* cyclization observed with **3** (Scheme 4), and is therefore not competing with the Nazarov cyclization.

Gratifyingly, treatment of **14** with 1.1 equivalents of $SnCl_4$ in CH_2Cl_2 at 0 °C (Table 2, entry 2) gave a new compound alongside **15**, the tricyclic **16** as product of the desired Nazarov/[3 + 2] tandem reaction. Attempts to optimize the cyclization conditions towards **16** through variation of Lewis acid equivalents and solvent were unsuccessful (Table 2, entries 3–7). However, an increased ratio of **16**:**15** was obtained when 10 mol% of $SnCl_4$ were used, with an overall yield of 23% of **16** based on recovered starting material (Table 2, entry 3).

The results confirmed that the intramolecular [3 + 2] cycloaddition is possible if the tether offers enough conformational



Scheme 6. Cyclization behavior of further functionalized precursors **10** and **12**. (a) $B(C_6F_5)_3 \cdot H_2O$ (1.1 equiv.), Et_2O , r.t., 1 h; (b) $B(C_6F_5)_3$ (7.5 mol%), toluene, r.t., 8.5 h.

Table 2. Tested conditions for cyclization precursor **14**.

Entry	Lewis acid	Conditions	Product (Yield ^[a])
1	$B(C_6F_5)_3$ (2.5 mol%)	CH_2Cl_2 , 30 °C, 8.5 h	15 (77%)
2	$SnCl_4$ (1.1 equiv.)	CH_2Cl_2 , –78 °C to 0 °C, 2 h	15 (25%), 16 (19%)
3	$SnCl_4$ (10 mol%)	CH_2Cl_2 , –78 °C to 0 °C, 4 d	15 (21%), 16 (15%), 14 (36%)
4	$SnCl_4$ (20 mol%)	CH_2Cl_2 , –78 °C to 0 °C, 2 d	15 (26%), 16 (< 5%)
5	$SnCl_4$ (30 mol%) ^[b]	CH_2Cl_2 , –78 °C to 0 °C, 6 h	15 (43%), 16 (1%)
6	$SnCl_4$ (1.1 equiv.)	toluene, –78 °C to 0 °C, 4 d	15 (45%)
7	$SnCl_4$ (1.1 equiv.)	$CHCl_3$, –78 °C to 0 °C, 4 h	15 (37%), 16 (< 5%)

[a] Isolated yield. [b] 0.1 equiv. were added every two hours.

flexibility during olefin-cation approach, but also showed that the spiro cyclization is generally preferred.

The observation of the spirocyclizations, acting as a leitmotif throughout our investigations, prompted us to revise and deeper investigate the mechanism of this reaction. The cyclization results of **10** and **12** had demonstrated that the spirocycle formation involves transposition of the side chain's double bond to the former (*E*)-methyl group (Scheme 6). Additionally, the very distinct relative stereochemistry at the α -position of the cyclization products (**8**, **11**, **13** and **15**) led to the suggestion that the reaction between the initially formed oxyallyl cation **C** and the tethered alkene proceeds through an ene-type mechanism (Scheme 7, I).^[12,21]

In order to evaluate this hypothesis we designed cyclization precursor **17** with a perdeuterated (*E*)-methyl group. Exposure to our catalytic cyclization conditions afforded deuterated spirocycle **18** as major product with selective deuterium incorporation at position 2. This validated our proposal of the Nazarov/ene-cyclization cascade as prevailing reaction mechanism (see Supporting Information for more detailed discussion).

To probe whether intermolecular proton/deuteron transfer can be observed as a competing reaction pathway, we performed a cross-over experiment, in which a mixture of undeuterated trienone **14** and its deuterated congener **17** was subjected to the cyclization. The intermolecular transfer would be expected to result in statistical protonation or deuteration of the enol moiety in intermediate **D** (Scheme 5), and lead to cross-over products **19** and **20** (Scheme 7). Mass spectrometric analysis of the product mixture showed that these products were not formed (see Supporting Information). This result ruled out intermolecular proton transfer as relevant process for the observed spirocyclizations, and so unambiguously confirmed that a Nazarov cyclization/ene-cyclization cascade is operating.

In summary, we performed cyclization experiments on five different trienones, differentiated by length of the side chain and functionalities, and obtained a small library of compounds,

which gave a first glance at the divergent reactivities that these substrates can exhibit. In particular, we were pleased to observe a recurring skeleton, which was shown to be the result of a novel interrupted Nazarov reaction, in which the carbocationic intermediate is trapped by an ene-type cyclization. This novel, up to now unreported tandem reaction allows for new synthetic approaches for the synthesis of complex natural products. Its application in total synthetic context is subject of ongoing efforts in our laboratories.

Acknowledgements

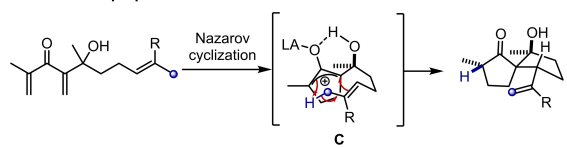
We thank Dr. J. Fohrer, M. Rettstadt and D. Körtje for detailed NMR analysis and Dr. G. Dräger, A. Schulz and R. Reichel for mass spectra. We thank A. Eggert, Y. Linne and L. Millbrodt for assisting in the preparation of the manuscript. C. E. thanks Dr. E. A. Stempel for support in the early stages of the project. Open access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

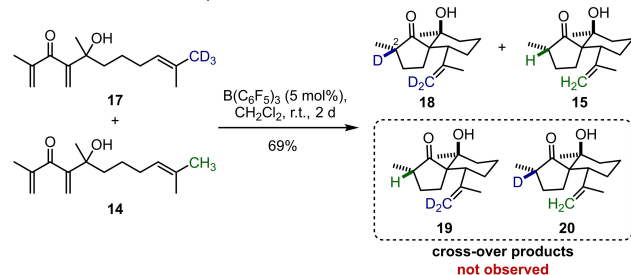
Keywords: cyclization · domino reactions · ene reaction · Nazarov cyclization · spiro compounds

I. Mechanistic proposal



II. Deuterium labeling studies

Proton/deuteron cross-over experiment



Scheme 7. Mechanistic proposal for the observed interrupted Nazarov cyclization leading to spiro compounds, and deuterium labelling studies in support of the proposal.

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