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Unprecedented Cobalt-Catalyzed Isomerization Reactions to Single Skipped 2,4,7-Trienes Applied in the Synthesis of Urushiol

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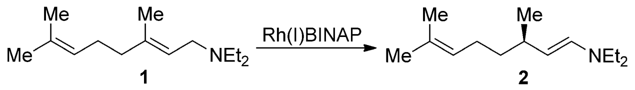
Abstract: The cobalt-catalyzed isomerization of 1,3-dienes to 2*Z*,4*E*-dienes was realized for the very challenging substrates with an additional double bond in the side chain. An isomerization to the conjugated 3,5,7-triene derivative was not observed, which is in stark contrast to observations with many other isomerization catalysts. Accordingly, the synthesis of the natural product urushiol, which has a sensitive 2*Z*,4*E*,7*Z*-triene subunit in the side chain, was investigated. The O-protected urushiol derivative was generated selectively without isomerization to the conjugated 3,5,7-triene or *Z*/*E*-isomerization of the double bond at position 7.

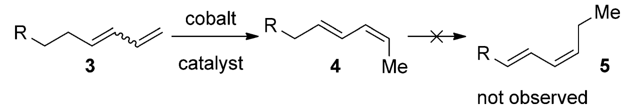
The isomerization of the configuration as well as the migration of double bonds are reactions where in sum neither a new bond is formed nor any atom is added or lost in the products. However, these reactions can be very useful in organic synthesis, particularly when the isomerization or the migration of double bonds starts from readily available starting materials and leads to more valuable products. In general, the formation of the thermodynamically more stable isomer is the predominant driving force. Accordingly, the isomerization of an alkene from the *Z*-configuration to the *E*-alkene has been disclosed several times[1] while the reverse reaction is more challenging.[2] For double bond migration reactions the thermodynamic driving force can be either a higher degree of substitution or the formation of a more stable double bond, such as those in carbonyl groups, imines or to double bonds which are then in conjugation to another unsaturated functionality.[3] One of the benchmark transformations in this respect is the asymmetric isomerization of the allylic amine **1** by chiral rhodium complexes for the formation of the chiral enamine **2** in the synthesis of the tocopherol side-chain as described by Noyori and co-workers (Scheme 1).[4]



Scheme 1. Asymmetric rhodium-catalyzed isomerization of an internal allylic amine into a chiral enamine.

Recently, Weix, Holland and co-workers described an outstanding application of a cobalt-catalyzed isomerization in which terminal alkenes were isomerized to the 2*Z*-alkenes as the major products.[5]

Prior to this publication, we reported the stereoselective cobalt-catalyzed isomerization of the *E*/*Z*-mixtures of 1,3-dienes **3** to the 2*Z*,4*E*-isomers **4**.[6] Remarkably, a further isomerization of the double bonds to the corresponding 3,5-dienes **5** were not observed (Scheme 2).



Scheme 2. Cobalt-catalyzed isomerization of terminal 1,3-dienes to **4**.

In the course of our ongoing investigation concerning cobalt-catalyzed isomerization reactions of 1,3-dienes, we identified the urushiol **6**,[7] a main component of East Asian lacquer (japanese: urushi),[8] as a highly interesting benchmark target molecule. Lacquerware has been used in East Asia for thousands of years for the preservation of wooden materials that can be found in everyday items as well as for decorative purposes. The main components of the non-polymerized lacquer have been identified to consist of catechol derivatives with a long side chain that show different grades of unsaturation. By far the highest content (up to 67 %) of such derivatives in urushiol was assigned to the 2*Z*,4*E*,7*Z*-isomer **6** shown in Figure 1.

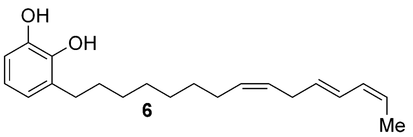


Figure 1. Structure of **6**, the main component of urushiol.[8c]

The synthesis of urushiol **6** from a corresponding 1,3,7-triene, such as **7**, implies specific challenges (Scheme 3): 1) The cobalt catalyst should isomerize the terminal 1,3-

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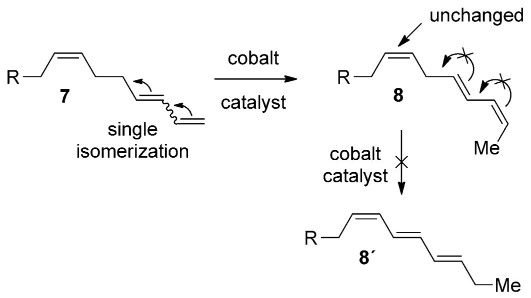
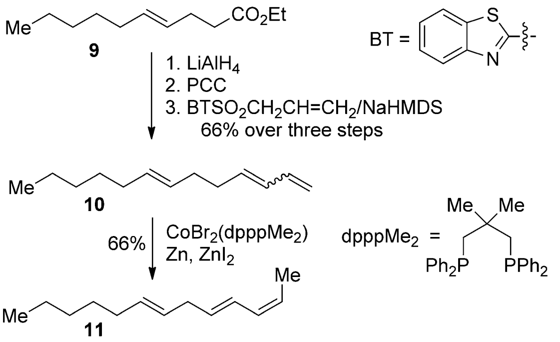


Scheme 3. Outline of the desired transformation of the terminal 1,3-diene subunit in **7** to the single skipped triene **8**.

diene subunit to the desired 2*Z*,4*E*-moiety. 2) A further isomerization to the thermodynamically more favored conjugated 3,5,7-triene in **8** has to be avoided. 3) The 7*Z*-double bond should not be altered by the cobalt catalyst, neither in its position nor in its configuration.

Before addressing the synthesis of urushiol **6**, we decided to examine the cobalt-catalyzed isomerization reaction on simple, easily accessible substrates. For this purpose, the triene **10** with an internal *E*-double bond was synthesized as outlined in Scheme 4. The commercially available ester **9** was reduced to the corresponding alcohol and transformed into the aldehyde through pyridinium chlorochromate (PCC) oxidation. The synthesis of the 1,3-diene was realized in a Julia–Kocienski olefination with 2-(allylsulfonyl)benzothiazole and sodium hexamethyldisilazane (NaHMDS) to afford **10** as a *E*/*Z*-mixture (*E*:*Z*=10:7) in 66% overall yield.

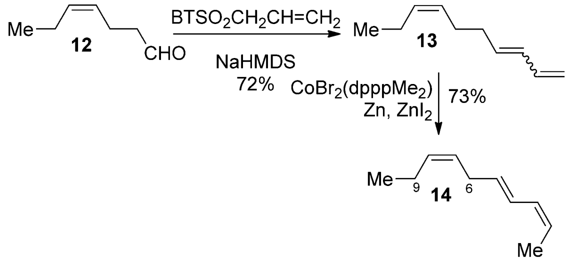


Scheme 4. Synthesis of 7*E*-10 and isomerization towards triene **11**.

The isomerization reaction of **10** was performed with the previously described cobalt catalyst system comprising $CoBr_2(dpppMe_2)$,[9] zinc powder, and zinc iodide in dichloromethane at ambient temperature to generate the triene **11**. After a reaction time of 14 h, complete conversion and the formation of a single new product was detected through GC/MS analysis. The desired product **11** was isolated after column chromatography in 66% yield.

The configuration of the 2*Z*- and the 4*E*-double bond could be unambiguously assigned by ^{1}H NMR coupling constants and is in accordance with the previously reported results.[6] The determination of the *E*-configuration of double bond 7 by ^{1}H NMR spectroscopic analysis could not be accomplished because the ^{1}H NMR resonances were overlapping and coupling constants could not be deduced. The configuration of double bond 7 was assigned based on the ^{13}C NMR specroscopic data since the ^{13}C NMR chemical shifts of the carbon atoms adjacent to the double bond in **11** are an excellent measure for the assignment of the 7*E*-double-bond configuration: C6: 36.0 ppm; C9: 32.7 ppm.[10]

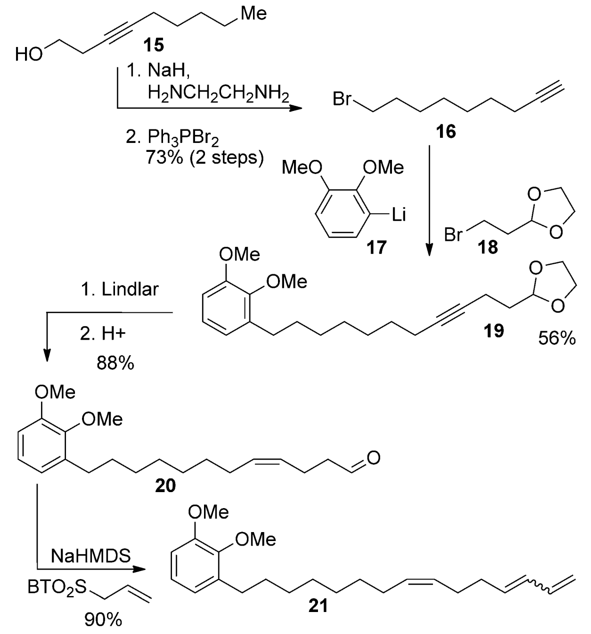
We then turned our attention to a more challenging triene with an internal *Z*-configured double bond (Scheme 5). Therefore, the commercially available aldehyde **12** was selected and transformed in a Julia-Kocienski olefination into the *E*/*Z*-mixture of triene **13** in 72% yield (*E*:*Z*=5:4).



Scheme 5. Synthesis of 7*Z*-configured **13** and isomerization towards triene **14**.

The cobalt-catalyzed migration afforded the desired triene **14** in 73% yield as a single product. As before, the configuration of double bond 7 could not be deduced from ^{1}H NMR coupling constants. The analysis of ^{13}C NMR data of **14** for C6 (30.7 ppm) and C9 (20.7 ppm) confirms the unchanged 7*Z*-double bond configuration. Accordingly, this data analysis revealed that the requirements outlined before for the double-bond migration were fulfilled. Firstly, the 1,3-diene unit migrated selectively to the 2*Z*,4*E*-position and configuration, and secondly the configuration and position of the double bond 7 remained unchanged.

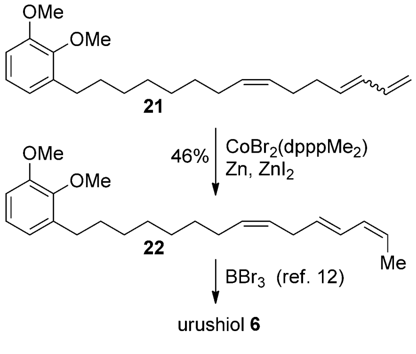
With these promising results in hand, we investigated the synthesis of the natural product, urushiol **6**. The precursor **21** for the cobalt-catalyzed isomerization reaction was obtained in a straightforward reaction sequence outlined in Scheme 6. Starting from the commercially available alkyne **15**, the triple bond was migrated to the terminal position applying a procedure described by Brown followed by an Appel bromination to afford the bromo-alkyne **16** in a good overall yield of 73%. In a one-pot reaction sequence, the bromo-alkyne **16** was treated with an excess of the *ortho*-lithiated catechol **17** (3.5 equiv), thus leading to the carbon–carbon bond formation and the deprotonation of the terminal alkyne proton: Subsequently, the second carbon–carbon bond formation was realized by addition of the alkyl bromide derivative **18**. The internal alkyne **19** was obtained in an acceptable yield of 56% with respect to the starting



Scheme 6. Synthesis of the 1,3,7-triene **21**.

alkyne **16**. The internal *Z*-configured double bond at position 7 of the side chain of the natural product was generated via Lindlar hydrogenation, and acidic deprotection of the acetal group afforded the aldehyde **20** in 88% yield over two steps. The terminal 1,3-diene in **21** was then introduced by a Julia-Kocienski olefination with 2-(allylsulfonyl)benzothiazole, and the desired 1,3,7-triene **21** (*E*:*Z* = 5:3) was obtained in 90% yield. Accordingly, the precursor for the cobalt-catalyzed isomerization/migration reaction, 1,3,7-triene **21**, was synthesized in 32% overall yield in only six steps.

The disclosed cobalt-catalyzed isomerization/migration afforded the desired O-protected 2*Z*,4*E*,7*Z*-triene **22** in 46% yield as a single product (Scheme 7).[11] The reduced yield of the O-protected natural product can be explained with accompanied polymerization. The ^{13}C NMR spectroscopic data of **22** (C6: 30.8 ppm; C9: 27.3 ppm) are in very good agreement with the reported data of the O-deprotected natural product (C6: 30.7 ppm; C9: 27.3 ppm).[12a] Therefore, the main task for the synthesis of the skipped triene subunit was accomplished.



Scheme 7. Isomerization of the 1,3,7-triene **21** to afford the O-protected urushiol derivative **22**.

The deprotection of the catechol moiety utilizing BBr_3 was described by Miyakoshi and co-workers for the synthesis of minor components of urushiol.[12b] However, the deprotected urushiol **6** is reported to be an extremely hazardous material and, therefore, the deprotection step was deliberately not performed. The O-protected derivative **22** did not cause any health problems to the persons involved, either directly or indirectly, with the synthesis of **22**.

Caution: Urushioles are also components of the so-called poison ivy plant (*Toxicodendron radicans*)[13] and cause dermatitis by allergic reactions to many people. In some cases, the contact with the plant even leads to anaphylaxis.[14]

In conclusion, we presented a very mild cobalt-catalyzed method for the isomerization/migration of 1,3-dienes to the corresponding 2*Z*,4*E*-dienes with an additional double bond in position 7. The cobalt-catalyzed isomerization did not proceed further to yield conjugated 3,5,7-trienes. Additionally, the configuration of the isolated double bond at position 7 was not altered as was deduced from comparison of ^{13}C NMR data with reported values for such materials. Finally, the cobalt-catalyzed isomerization reaction was applied as the key step in the synthesis of the O-protected main component of urushiol **6**, with the challenging skipped 2*Z*,4*E*,7*Z*-subunit.

Experimental Section

Experimental Details for the Isomerization Reaction

Anhydrous zinc iodide (20 mol%), zinc powder (20 mol%), and $Co(dpppMe_2)Br_2$ (10 mol%) were suspended in anhydrous dichloromethane under an argon atmosphere in a flame dried Schlenk tube fitted with a Teflon screw cap. Subsequently, the *E*/*Z*-mixture of the 1,3,7-triene (final conc. 1.0 M) was added and the reaction mixture was stirred at room temperature until complete conversion of the starting material was observed (GC/MS analysis). The reaction mixture was then filtered over a short pad of silica gel with pentane as eluent. The solvent of the eluate was then removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel with pentane as eluent.

Keywords: 1,3-dienes • cobalt • isomerization • stereoselectivity • urushiol

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[1] a) M. Mayer, A. Welther, A. Jacobi von Wangelin, *ChemCatChem* **2011**, *3*, 1567; b) W. Tsuzuki, *Chem. Phys. Lipids* **2010**, *163*, 741; c) D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard, T. Skrydstrup, *J. Am. Chem. Soc.* **2010**, *132*, 7998; d) G. Erdogan, D. B. Grotjahn, *J. Am. Chem. Soc.* **2009**, *131*, 10354; e) N. Catozzi, M. G. Edwards, S. A. Raw, P. Wasnaire, R. J. K. Taylor, *J. Org. Chem.* **2009**, *74*, 8343; f) C. Ferreri, M. Panagiotaki, C. Chatgilialoglu, *Mol. Biotechnol.* **2007**, *37*, 19; g) T. J. Donohoe, T. J. C. O'Riordan, C. P. Rosa, *Angew. Chem.* **2009**, *121*, 1032; *Angew. Chem. Int. Ed.* **2009**, *48*, 1014; h) R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27; i) M. Mirza-Aghayan, R. Boukherroub, M. Bolourtchian, M. Hosei-

ni, K. Tabar-Hydar, *J. Organomet. Chem.* **2003**, *678*, 1; j) I. R. Baxendale, A.-L. Lee, S. V. Ley, *Synlett* **2002**, 516.

[2] a) F.-L. Wu, B. P. Ross, R. P. McGeary, *Eur. J. Org. Chem.* **2010**, 1989; b) H. Firouzabadi, N. Iranpoor, M. Jafarpour, *Tetrahedron Lett.* **2005**, *46*, 4107; c) M. T. Reetz, M. Plachky, *Synthesis* **1976**, 199.

[3] a) S. Krompiec, M. Krompiec, R. Penczek, H. Ignasiak, *Coord. Chem. Rev.* **2008**, *252*, 1819; b) N. Kuźnik, S. Krompiec, *Coord. Chem. Rev.* **2007**, *251*, 222; c) S. Krompiec, R. Penczek, M. Krompiec, T. Pluta, H. Ignasiak, A. Kita, S. Michalik, M. Matlengiewicz, M. Filapek, *Curr. Org. Chem.* **2009**, *13*, 896; d) A. Philippaerts, S. Goossens, P. A. Jacobs, B. F. Sels, *ChemSusChem* **2011**, *4*, 684.

[4] K. Tani, T. Yamagata, S. Otsuka, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, *J. Chem. Soc. Chem. Commun.* **1982**, 600.

[5] C. Chen, T. R. Dugan, W. W. Brennessel, D. J. Weix, P. L. Holland, *J. Am. Chem. Soc.* **2014**, *136*, 945.

[6] F. Pünner, A. Schmidt, G. Hilt, *Angew. Chem.* **2012**, *124*, 1296; *Angew. Chem. Int. Ed.* **2012**, *51*, 1270.

[7] a) O. Vogl, *J. Polym. Sci. Part A* **2000**, *38*, 4327, and references therein; b) Y. Yamauchi, R. Oshima, J. Kumanotani, *J. Chromatography* **1982**, *243*, 71; c) S. Billets, M. D. Craig, M. D. Corbett, J. F. Vickery, *Phytochemistry* **1976**, *15*, 533.

[8] a) R. Lu, T. Yoshida, T. Miyakoshi, *Polym. Rev.* **2013**, *53*, 153; b) H. S. Kim, J. H. Yeum, S. W. Choi, J. Y. Lee, I. W. Cheong, *Prog. Org. Coat.* **2009**, *65*, 341; c) J. Kumanotani, *Prog. Org. Coat.* **1995**, *26*, 163.

[9] dpppMe$_2$ = 2,2-dimethylpropane-1,3-diyl)bis(di-phenylphosphine).

[10] H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A. Washenfelder, D. A. Bussmann, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 58.

[11] The desired product **22** could be obtained in up to 67% yield on a 0.08 mmol scale.

[12] a) S. Harigaya, T. Honda, L. Rong, T. Miyakoshi, C.-L. Chen, *J. Agric. Food Chem.* **2007**, *55*, 2201; b) T. Miyakoshi, H. Kobuchi, N. Niimura, Y. Yoshihiro, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2560. As alternative for the deprotection of arylmethyl ethers, NaSEt was applied successfully; see: c) A. B. Smith III, S. R. Schow, J. D. Bloom, A. S. Thompson, K. N. Winzenberg, *J. Am. Chem. Soc.* **1982**, *104*, 4015.

[13] a) K. H. Lee, J. K. K. Ho, K. M. Lam, W. Y. Wu, *Hong Kong J. Emergency Med.* **2011**, *18*, 335; b) S. Schauder, R. Callauch, B. M. Hausen, *Hautarzt* **2006**, *57*, 618.

[14] R. S. Kalish, J. A. Wood, A. LaPorte, *J. Clin. Invest.* **1994**, *93*, 2039.

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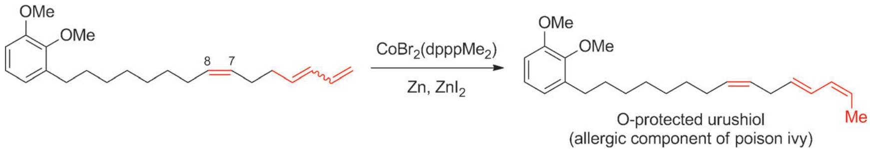

My heart skipped, skipped a beat: The skipped 2,4,7-triene subunit of urushiol was generated from the 1,3,7-triene through a cobalt-catalyzed isomerization reaction in a stereoselective fashion. The double bond configuration of the double bond at position 7 remained unchanged whereas the 2*Z*,4*E*-configuration was controlled by the cobalt catalyst.

Isomerization

Anastasia Schmidt,
*Gerhard Hilt** ________ ■■■■–■■■■

Unprecedented Cobalt-Catalyzed Isomerization Reactions to Single Skipped 2,4,7-Trienes Applied in the Synthesis of Urushiol