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First Total Synthesis of *trans*- and *cis*-Resorcylide: Remarkable Hydrogen-Bond-Controlled, Stereospecific Ring-Closing Metathesis

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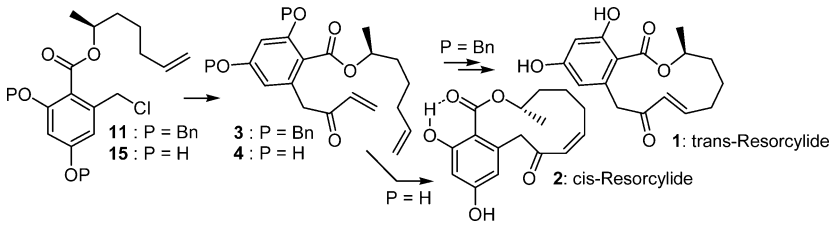
ABSTRACT



Stereospecific synthesis of the pair of natural macrolides, *trans*- and *cis*-resorcylide, was performed using ring-closing metathesis on dienes 3 and 4, which lack or feature an intramolecular H-bond, respectively. An effective Stille carbonylative coupling of benzyl chlorides 11 and 15 was employed for their preparation. The influence of intramolecular H-bonding on the interconversions of resorcylides was also studied.

Trans- and *cis*-resorcylide are both natural macrocyclic plant growth inhibitors, isolated independently from different *Penicillium* species.[1] Along with zearalenone,[2] lasiodiplodin,[3] and the important antitumor agent radicicol,[4] they constitute an important class of bioactive resorcylic macrolides. Furthermore, they are structurally closely related to the new class of anticancer compounds salicylihalamides[5] and oximidines[6] (Figure 1).

Despite the great number of reports regarding the synthesis of all aforementioned natural products using ring-closing metathesis[7] (RCM), no study has been disclosed so far toward the stereoselective preparation of *trans*- or *cis*-resorcylide, although this pair of double-bond isomers consists an ideal substrate for exploration of the selectivity of medium-sized RCM cyclizations.[8] They possess a rather unique structural mark: the cis isomer is characterized by a strong H-bond between the phenol hydroxyl and the lactone carbonyl, while the trans isomer lacks that feature.[1a] One might assume that

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(3) (a) Lee, K.-H.; Hayashi, N.; Okano, M.; Hall, I. H.; Wu, R.-Y.; McPhail, A. T. *Phytochemistry* **1982**, *21*, 1119. (b) Cambie, R. C.; Lal, A. R.; Rutledge, P. S.; Woodgate, P. D. *Phytochemistry* **1991**, *30*, 287.

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(5) (a) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188. (b) For a review, see: Yet, L. *Chem. Rev.* **2003**, *103*, 4283.

(6) Kim, J. W.; Shin-ya, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153.

(7) Application of RCM in the synthesis of: (a) Zearalenone and lasiodiplodin: Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990. (b) Radicicol: Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903. (c) Salicylihalamides: (i) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731. (ii) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem.—Eur. J.* **2001**, *7*, 5286. (iii) Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817. (iv) Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245. (d) Oximidine II: Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040.

(8) For recent reviews on RCM, see: (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (d) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826.

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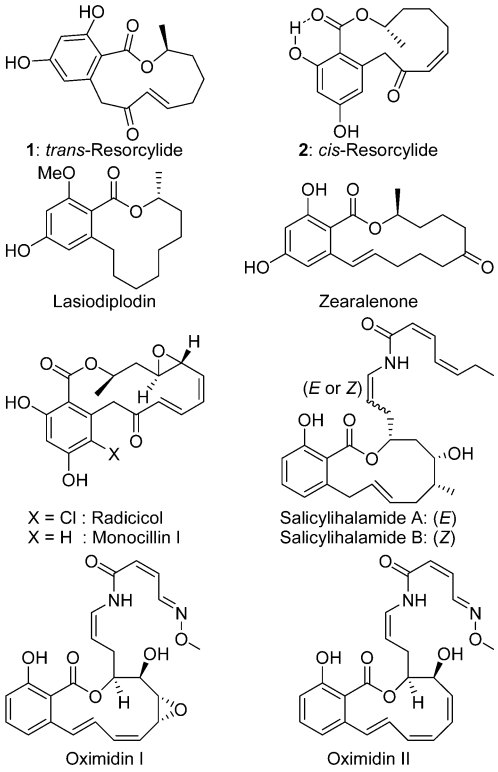


Figure 1. Structures of resorcylic and salicylic macrolides.

the observed thermodynamic preference for the cis isomer is associated with the H-bond, whereas the H-bond-free conformation favors the trans isomer.

The above association of the stereochemistry of the alkene moiety with the existence of the H-bond, as well as with the differences in relative thermodynamic stability of the two isomers, leads to dienes **3** and **4** as synthetic precursors (Figure 2). Taking into account that RCM reactions employing second-generation catalysts proceed under thermodynamic control,[9] it was anticipated that these two intermediates could provide access to either *trans*- or *cis*-resorcylide, stereoselectively. Thus, diene **4** was expected to feature an intramolecular H-bond, making it a potential precursor for the cis isomer, whereas its protected analogue **3**, devoid of this property, might lead to the trans isomer. This assumption is further strengthened by the prevailing aspect that the stereochemical outcome of RCM cyclizations is substrate-dependent, and even a subtle structural difference at a remote center of the molecule substantially influences the isomeric ratio of the products.[10] In diene **4**, H-bond "locks" a coplanar conformation between the aromatic moiety and the carboxylate plane, which is sterically forbidden in benzylated analogue **3**. This essential structural difference, being by far more severe than a mere alteration in a remote position, is expected to dramatically influence the behavior of the two precursors under RCM conditions.[11]

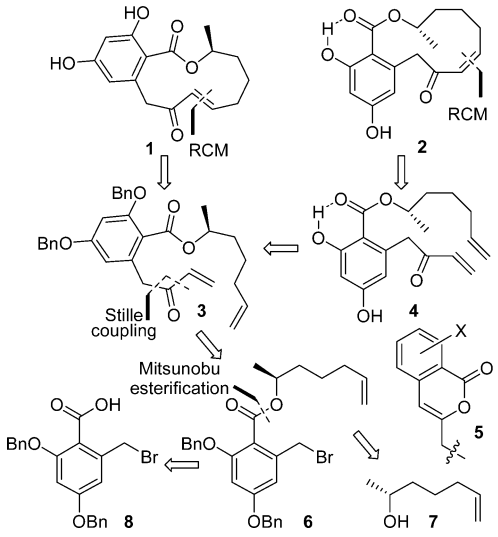


Figure 2. Retrosynthetic analysis of *trans*- and *cis*-resorcylide.

To complete the retrosynthetic scheme, one has also to consider the problem of the enolizable benzylic methylene group α- to the enone moiety. Under basic conditions, it tends to isomerize toward the related isocoumarin **5** (Figure 2), a complication already encountered toward the syntheses of related natural products.[7b,12] This issue was addressed with a straightforward disconnection employing a carbonylative Stille coupling[13] to secure the formation of diene **3** from ester **6** in one step under neutral conditions. Aromatic ester **6** may in turn be prepared from the known alcohol **7**[14] and the easily accessible benzoic acid derivative **8**, using Mitsunobu protocol.[15]

In practice, benzoic acid **10** (Scheme 1) was readily prepared within two steps from commercially available 3,5-dibenzyloxybenzyl alcohol **9**. Since **10** is prone to phthalide formation under classic Mitsunobu conditions, coupling with alcohol **7** was achieved applying Danishefsky's modified protocol[7b] to furnish ester **11** in high yield.[16] Successful carbonylative coupling of the latter with vinyl stannane afforded the designed diene **3** in acceptable yield.[17] Subjecting the above diene to RCM conditions employing second-generation Grubbs catalyst[18] (**I**), we were pleased to isolate the desired *trans*-alkene **12** as a sole isomer and in relatively high yield.

Unfortunately, all attempts to cleave the benzyl ethers were unsuccessful. To overcome this problem, a three-step sequence was employed. Michael acceptor enone moiety was masked by means of diphenyldiselenide,[19] and the resulting

(9) For an illustration of this aspect, see: Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061.

(10) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733.

(11) Previous H-bond influence on RCM has been observed (see ref 7c,i).

(12) Fürstner, A.; Castanet, A.-S.; Radkowski, K.; Lehmann, C. W. *J. Org. Chem.* **2003**, *68*, 1521.

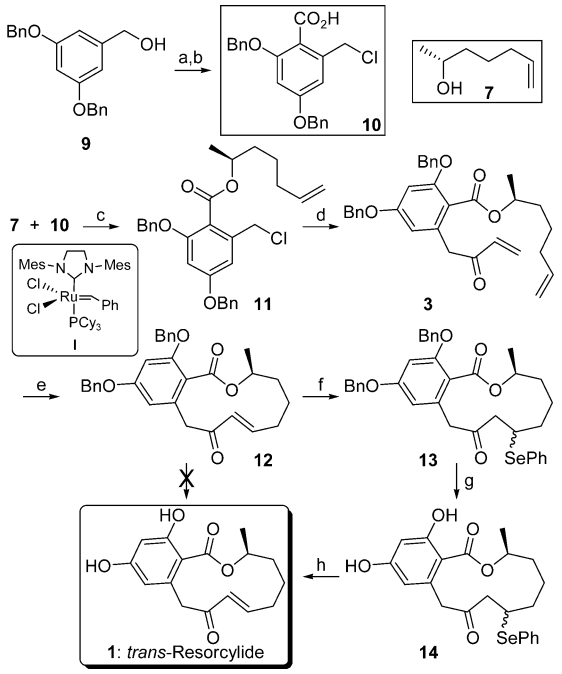
(13) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

(14) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155.

(15) Mitsunobu, O. *Synthesis* **1981**, *1*, 1.

(16) Inversion of configuration was ensured by hydrolysis of ester **11** under basic conditions (aq NaOH (30%), DMSO, 70 °C, 24 h, 60%) and measurement of the optical rotation power of the resulting alcohol.

Scheme 1. Synthesis of *trans*-Resorcylide[a]

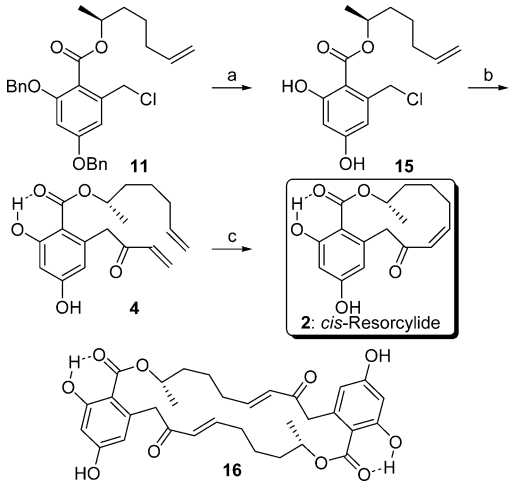


[a] Reagents and conditions: (a) $POCl_3$, DMF, 90 °C, 3 h, 90%; (b) $NaClO_2$, H_2NSO_3H, Acetone/DMSO/H_2O (5:2:5), 0 °C, 30 min, 95%; (c) DIAD, P(2-furyl)$_3$, benzene, rt, 15 min, 73%; (d) (*n*-Bu)$_3$SnCH=CH_2, CO, Pd(PPh$_3$)$_4$, P(2-furyl)$_3$, HMPA, 80 °C, 2 h, 60% (two cycles); (e) **I** (10 mol %), DCM (dilution 1 mM), reflux, 30 min, 67%; (f) Ph_2Se_2, $NaBH_4$, EtOH, AcOH, THF, rt, 10 min, 79%; (g) BBr_3/PhSMe, DCM, −78 °C, 30 min, 72%; (h) H_2O_2 (30%), AcOH, THF, H_2O, 0 °C, 1 h, 90%.

selenide **13** was subsequently treated with BBr_3/PhSMe to afford free diphenol **14** in good yield. The latter, after oxidation to the corresponding selenoxide and concomitant in situ kinetically stereocontrolled syn-elimination,[20] furnished *trans*-resorcylide **1** in high yield.

The encountered serious deprotection problems led us to reconsider the original strategy toward the cis isomer. Thus, dibenzyl ether **11** was first deprotected by means of BBr_3 to afford free resorcinol **15** in high yield (Scheme 2), which subsequently underwent Stille carbonylative coupling with vinyl stannane to form targeted intermediate diene **4** very effectively. Cyclization of diene **4**, however, was rather problematic compared to that of diene **3**. Only the combination of extremely high dilution, elevated temperature (80 °C, trichloroethane), and low catalyst loading enabled us to isolate *cis*-resorcylide **2** in reasonable yield, along with the head-to-tail, 24-membered macrocyclic dimer **16** (Scheme 2).

Scheme 2. Synthesis of *cis*-Resorcylide[a]



[a] Reagents and conditions: (a) BBr_3/PhSMe, DCM, −78 °C, 30 min, 85%; (b) (*n*-Bu)$_3$SnCH=CH_2, CO, Pd(PPh$_3$)$_4$, P(2-furyl)$_3$, HMPA, 80 °C, 90 min, 74%; (c) **I** (2 mol %), CCl_3CH_3 (dilution 0.5 m*M*), reflux, 1 h, 40% (along with 29% of dimer **16**).

Despite the low yield, the obtained stereospecificity was by far beyond our most optimistic expectations. Head-to-tail dimerizations as well as lower cyclization yields of similar electron-deficient alkenes such as acrylic acid derivatives have also been reported by Grubbs and Fürstner.[14,18a] However, to the best of our knowledge, this is the first example of RCM cyclizations employing enolizable enones such as **3** or **4**.

With both natural products available, we then decided to cast some light on their interconversions and thermodynamic stability. Thus, synthetic *trans*-resorcylide **1**, upon exposure to light or under acidic (HCl) conditions, was readily isomerized to the thermodynamically more stable *cis*-resorcylide **2**, in accordance to previous reports[1a,21] (Scheme 3). Furthermore, upon treatment with second-generation Grubbs catalyst and due to secondary metathetical isomerization,[22] **1** was rapidly isomerized to the same isomer **2**, which was further dimerized to macrolide **16**. One remaining question was the influence of intramolecular H-bonding on the behavior of these natural products. To address this question, protection and subsequent isomerization under RCM conditions was scheduled.[23] Surprisingly, *cis*-resorcylide **2** spontaneously isomerized during acetylation, resulting in *trans*-diacetate **17**.[24] This result is in accordance to

(17) The bromide originally designed is readily converted to the corresponding phthalide. The observed reactivity of the alternatively used benzyl chlorides **11** and **15** under Stille conditions is impressive and unprecedented.

(18) Presence of an electron-deficient double bond directly suggests this catalyst selection. For related examples, see: (a) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449. (b) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (c) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

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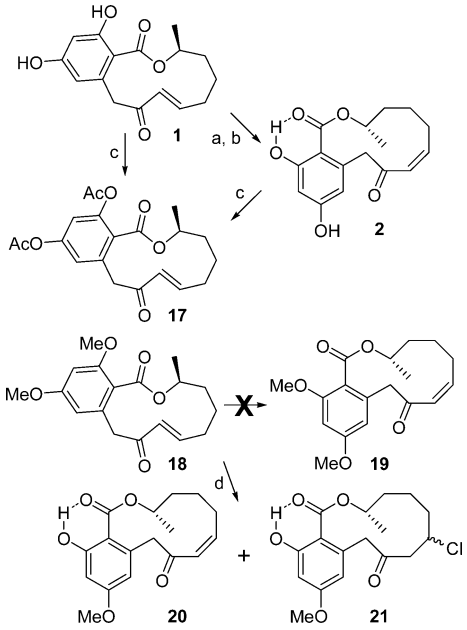
(21) Takahashi, T.; Minami, I.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 2651.

(22) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145 and references therein.

(23) *cis*-Resorcylide, not surprisingly, proved to be very difficult to protect. The H-bonded hydroxyl resisted reaction with benzylbromide or *t*-butyldimethylsilyl trifluoromethane-sulfonate (TBSOTf), whereas use of K_2CO_3 or 2,6-lutidine, respectively, led to the formation of isocoumarins. It also proved to be inactive under Mitsunobu conditions or against Schmidt's reagent (BnOC(=NH)CCl_3).

Scheme 3. Interconversions of Resorcylides[a]



[a] Reagents and conditions: (a) $h\nu$ or 2 N HCl; (b) [Ru] catalyst (5 mol %), CCl_3CH_3 (dilution 0.5 mM), reflux, 10 min, 39% (along with 28% of dimer **16**); (c) Ac_2O/pyr, rt, 18 h, 85%; (d) BCl_3, DCM, 30 min, −78 °C, 30% of **20** and 40% of **21**.

our original hypothesis that the intramolecular H-bond is the stereocontrolling element of this pair of natural products. Moreover, contrary to the apparent rapid isomerization of **1** under RCM conditions, the dimethyl analogue **18** did not isomerize even under prolonged reaction time and high catalyst loading, whereas it did "switch back" to the more stable cis form **20** upon BCl_3-induced partial deprotection! The isolation of adduct **21** out of this reaction mixture indicated that the observed isomerizations occurred most propably through reversible Michael-type additions.[25]

(24) Attempted deacetylation of **17** was also troublesome because of the formation of isocoumarins.

Thus, in retrospect, we realized that the three-step protocol used to synthesize *trans*-resorcylide **1** should indeed be the only way to construct this relatively unstable isomer, since deprotection in the presence of the double bond results in spontaneous isomerization and restoration of the H-bond. The observed "on−off" triggering effect of the H-bond on the stereochemistry of the double bond in this system is quite impressive.

In conclusion, a short and convergent total synthesis of *trans*- and *cis*-resorcylide was accomplished for the first time supporting the originally assigned absolute configuration.[1a] The enone functionality was efficiently constructed using Stille carbonylative coupling. Ring closing was achieved using second-generation Grubbs catalyst **I** (Scheme 1), while the stereochemistry of the resulting double bond was secured by altering the diene precursor conformation through control of the intramolecular H-bond.

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Note Added after ASAP Posting. There was an error in the structure of Ru catalyst **I** (Scheme 1) in the version posted ASAP February 14, 2004; the corrected version was posted March 2, 2004.

Supporting Information Available: Detailed descriptions of experimental procedures and characterization data for compounds **1**−**4** and **10**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Greater reactivity of the trans isomer towards nucleophiles has also been mentioned before; see: Sassa, T.; Manabu, N.; Michimasa, I. *Nippon Kagaku Kaishi* **1981**, *5*, 883.