

Stereoselective Synthesis of *E,Z*-Configured 1,3-Dienes by Ring-Closing Metathesis. Application to the Total Synthesis of Lactimidomycin

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S Supporting Information

ABSTRACT: Strategic positioning of a silyl group on the diene unit of a diene-ene substrate allows rigorous regio- and stereocontrol to be exerted during metathesis-based macrocyclization reactions. The versatility of this concise approach to *E,Z*-configured 1,3-dienes of ring sizes of 12 or larger is demonstrated by an application to the total synthesis of lactimidomycin, a potent translation and cell-migration inhibitor.

The formation of conjugated dienes or polyenes by ring-closing metathesis (RCM) remains a formidable challenge, as it requires rigorous control over the configuration of the newly formed double bond to be accorded with strict regiocontrol. Unfortunately, the currently available catalysts do not yet fully meet either demand.¹ Most notably, it remains difficult to discriminate between the two olefinic sites of a given 1,3-diene substrate. Activation of the internal double bond, however, results in ring contraction, which may become the dominant or even exclusive pathway. Although successful cases of metathetic diene (polyene) syntheses are known, the data shown in Table 1 are representative and echo the difficulties previously encountered in the literature.^{2,3}

Independent of the chosen catalyst and the conditions, substrate **1** was converted into mixtures consisting of three isomeric diene products **2** and both isomers of the ring contracted cycloalkene **3**. With the first generation catalyst **4a**, the diene was major but the product ratio not very encouraging; unsurprisingly, this mixture of five isomeric and/or homologous products was inseparable by flash chromatography. When the second generation Grubbs catalyst **4b** was used, ring contraction was already almost complete once the substrate was consumed (4 h). Additional control experiments with other substrates (Supporting Information) showed the exact same trends; in no case investigated was a single 1,3-diene isomer formed exclusively.

The prevalence of macrocyclic dienes in nature makes a more reliable approach highly desirable. We were particularly keen on gaining access to *E,Z*-dienes, which are a recurrent motif in bioactive natural products as witnessed by the few selected examples shown in Chart 1. To this end, a multitasking C-silylation strategy was envisaged, based on the notion that a suitably located silyl substituent should protect the internal double bond against attack by Grubbs-type complexes and hence effectively cut off the undesirable ring contraction.^{4,5} At the same time, a bulky R₃Si group was expected to exert a

significant stereodirecting effect, provided that the [2 + 2]-cycloaddition step generates a trigonal bipyramidal metallacyclic intermediate of the kind observed with small alkenes as the substrates (Scheme 1).^{6,7} Under this premise, one can anticipate that intermediate **A** is clearly favored over isomer **B**, which suffers from severe nonbonding interactions between the silyl residue and the alkyl chain R¹ (which is tethered to R² in the case of macrocyclizations); a concerted cycloreversion of **A** leads to products of type **C**, which upon protodesilylation afford the desired *E,Z*-dienes **D**.⁸ In view of the popularity of O-silyl groups in target oriented synthesis, it is likely that the necessary desilylation at carbon can be performed concomitant with the standard O-deprotections and will hence not increase the step count in many conceivable applications of this methodology. Moreover, a C-silyl substituent opens many additional possibilities for postmetathetic transformations other than protodesilylation, most notably via oxidative cleavage or cross coupling (see below). This outlook dictated the choice of BnMe₂Si,⁹ (2-thienyl)Me₂Si,^{10a,b} or PhMe₂Si groups^{10c} in our studies, all of which turned out to entail the exact same stereochemical consequences for the RCM reactions.

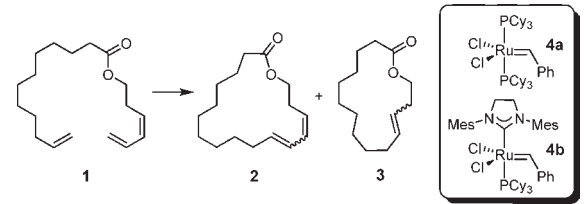
Although the rationale outlined above is certainly oversimplified and does not account for any conformational effects imposed on the stereodetermining step by the emerging macrocycle, we were pleased to see that the outcome of a representative set of model reactions matched our expectations very well (Scheme 2). Using **6** as a sufficiently active catalyst,¹¹ substrate **5**¹² and analogues reacted solely at the terminal olefins, leaving the silylated alkene site untouched; the newly formed double bonds were invariably *E*-configured according to NMR and GC/MS. Once the macrocycle is closed, the double bond geometry is effectively locked; even resubjection of the isolated compound **7a** to a fresh catalyst and stirring of the mixture in refluxing toluene for 20 h under an atmosphere of ethylene did not lead to the formation of any isomers, as judged by GC and NMR (only small amounts of ring opening with formation of substrate **5a** were detected, ca. 8% after 20 h). This control experiment confirms the effectiveness of the silyl substituent as a protecting and directing group alike.

As can be seen from the examples compiled in Scheme 2, this pattern was independent of the ring size as well as of the tether length between the reacting sites and the polar substituents. The isolated yields were good to excellent, except for the highly strained 12-membered lactone **10** which was formed somewhat

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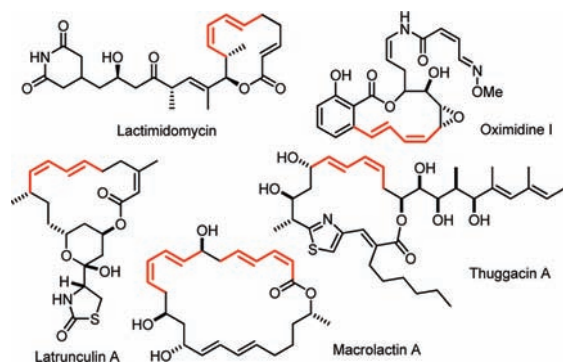
Table 1. Ring Contraction Interfering with an Attempted RCM-based 1,3-Diene Synthesis^a



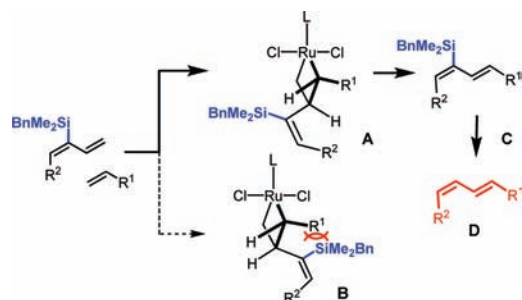
No.	Cat.	T (°C)	t (h)	2 (dr) ^b	3 (dr)
1	4a	20	24	86% (<u>3</u> :1:1)	14% (5:1)
2	4a	110 ^c	22	91% (<u>2.7</u> :1:1)	9% (5:1)
3	4b	20	4	<5%	95% (7:1)
4	4b	110 ^c	4	12% (<u>1</u> :3:4)	88% (6:1)

^a All reactions were performed in toluene (*c* = 2 mM) with 10 mol % catalyst loading. ^b The underlined number shows the ratio of the desired *E,Z*-isomer in the crude mixture as determined by GC; the assignment was made by comparison with the authentic material prepared as described below. ^c In the presence of C₃P=O (10 mol %).

Chart 1. Selected Macrolides Containing *E,Z*-Diene Motifs

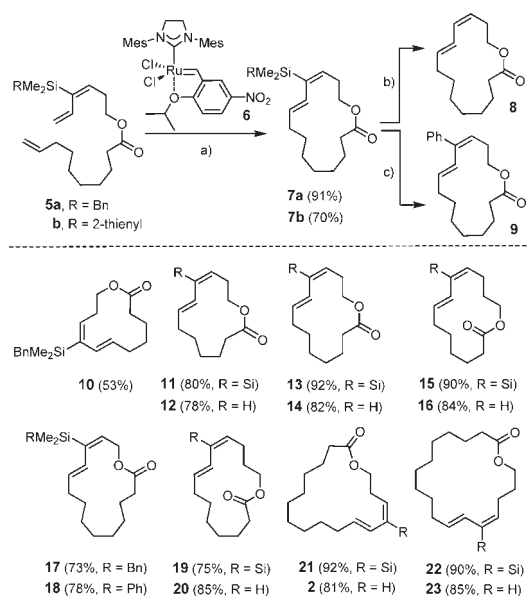


Scheme 1. A Silyl Substituent as a Protecting and Stereodirecting Group; L = C₃P or N-Heterocyclic Carbene



less efficiently (53%). It is of note, however, that this and the other entries were not fully optimized; as will be shown below, a proper choice of catalyst allows significantly better yields to be obtained even for more congested 12-membered rings. However, it was mandatory to run the reactions in the presence of catalytic amounts of C₃P=O¹³ or tetrafluoro-*p*-quinone¹⁴ as additives to keep the amount of double bond isomerization prior to ring

Scheme 2. Silyl-Directed Synthesis of Macrocyclic *E,Z*-Configured 1,3-Dienes^a



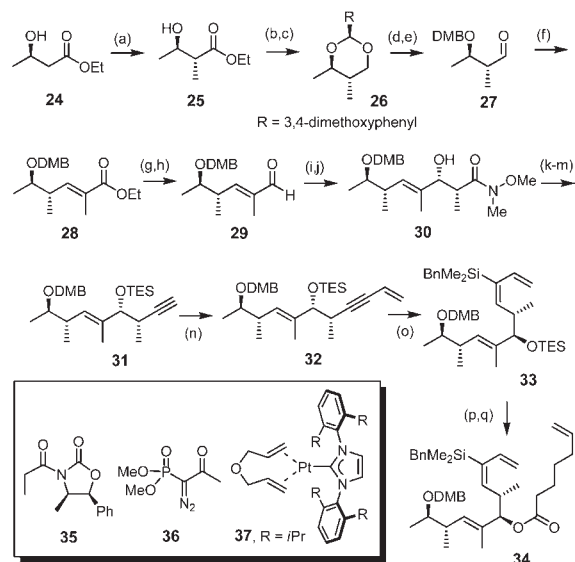
^a Reagents and conditions: (a) **6** (10 mol %, slowly added), C₃P=O (10 mol %), toluene, 60 °C; (b) TBAF, THF, 85%; (c) (i) TBAF · 3H₂O, THF; (ii) Ph-I, Pd₂(dba)₃ · CHCl₃ (5 mol %), THF, 78% (from **7b**). Products **10**–**23** were obtained analogously by RCM and protodesilylation; Si = SiMe₂Bn.

closure at a tolerable level (≤5%).¹⁵ As expected, the protodesilylation of the primary products with the aid of TBAF occurred smoothly, as did a prototype Hiyama–Denmark type cross-coupling reaction¹⁶ with iodobenzene as the model substrate (Scheme 2).

Next, we sought to scrutinize the methodology by an application to the total synthesis of lactimidomycin.¹⁷ As the formation of the 12-membered lactone **10** had been the least efficient among all model compounds investigated, the equally 12-membered core of this natural product represented a particularly stringent test. At the same time, lactimidomycin is a highly valuable material: this compound not only exhibits appreciable antiproliferative properties *in vivo* against various tumors including the highly invasive MDA MB 231 human breast adenocarcinoma^{17,18} but also constitutes an important lead structure in the quest for small molecule inhibitors of cell migration, which may ultimately serve to combat metastasis.¹⁹ In this regard, lactimidomycin seems to rival or even surpass the well investigated migrastatin family in potency, although its mode of action may be different at the molecular level.²⁰

Adol **24** served as the point of departure, which was elaborated into the known aldehyde **29** according to a route previously described in the literature (Scheme 3).²¹ A subsequent Evans boron aldol reaction²² followed by removal of the auxiliary gave Weinreb amide **30**, which was reduced with Dibal-H, and the resulting aldehyde converted to enyne **32** with the aid of the Ohira–Bestmann reagent **36**²³ followed by a Sonogashira coupling with vinyl bromide.²⁴

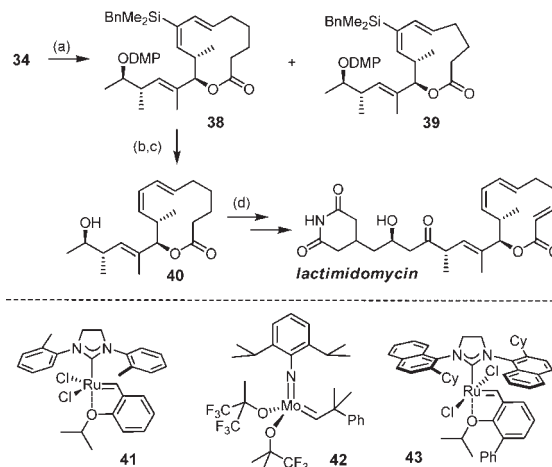
We were pleased to note that the hydrosilylation of this compound catalyzed by the platinum carbene complex **37**²⁵

Scheme 3^a

^a Reagents and conditions: (a) LDA, MeI, THF/HMPA, $-78\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$, 92%; (b) LiAlH_4 , Et_2O , $0\text{ }^{\circ}\text{C}$; (c) $(\text{MeO})_2\text{C}_6\text{H}_3\text{CHO}$, $p\text{TsOH}$ cat., benzene, $80\text{ }^{\circ}\text{C}$, 65% (over both steps); (d) Dibal-H, CH_2Cl_2 , $-50\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$, 98%; (e) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , $-78\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$, 99%; (f) $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{COOEt}$, CH_2Cl_2 , 93%; (g) Dibal-H, CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$; (h) $\text{SO}_3 \cdot \text{pyridine}$, DMSO, Et_3N , CH_2Cl_2 , 82% (over both steps); (i) **35**, Bu_2BOTf , Et_3N , CH_2Cl_2 , $-78\text{ }^{\circ}\text{C} \rightarrow \text{RT}$, 95%; (j) $\text{MeNH}(\text{OMe}) \cdot \text{HCl}$, Me_3Al , THF, $-20\text{ }^{\circ}\text{C} \rightarrow \text{RT}$, 90%; (k) TESOTf, 2,6-lutidine, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 90%; (l) Dibal-H, THF, $-78\text{ }^{\circ}\text{C}$; (m) **36**, K_2CO_3 , MeOH, $0\text{ }^{\circ}\text{C} \rightarrow \text{RT}$, 76% (over both steps); (n) $\text{H}_2\text{C}=\text{CHBr}$, CuI, $(\text{PPh}_3)_2\text{PdCl}_2$ (5 mol %), $i\text{Pr}_2\text{NH}$, THF, 88%; (o) **37** (1 mol %), BnMe_2SiH (3 equiv), 93% (dr = 96:4); (p) PPTS cat., EtOH, 89%; (q) 6-heptenoic acid, EDC \cdot HCl, DMAP, CH_2Cl_2 , $0\text{ }^{\circ}\text{C} \rightarrow \text{RT}$, 97%.

proceeded with a remarkable level of regiocontrol to give the desired product **33**. The reaction was best performed neat, using an excess of the silane; under these conditions, the required isomer was consistently obtained in excellent yield with $\geq 95:5$ selectivity. Although the hydrosilylation of alkynes in general has been intensely studied,²⁶ applications to such conjugated enynes are essentially missing; the case presented herein, however, encourages a more comprehensive study.

Cleavage of the TES-ether in **33** followed by esterification of the resulting alcohol with 6-heptenoic acid set the stage for the metathetic closure of the elaborate macrocycle. Under the standard conditions of the model series using complex **6**¹¹ as the catalyst, the desired product **38** was obtained in moderate yield, contaminated with significant amounts of the 11-membered homologue **39**, which could not be removed by flash chromatography (Scheme 4). The reluctance of **34** to form the highly strained product gives alkene isomerization a chance to compete with productive RCM and explains the partial loss of one methylene unit from the tether.¹⁵ Replacement of catalyst **6** by the somewhat slimmer complex **41**,²⁷ designed for metathesis reactions of sterically hindered substrates, gave rather poor results, whereas the molybdenum alkylidene **42**²⁸ furnished only dimeric products (Table 2). Gratifyingly though, the use of the more encumbered ruthenium carbene **43** recently reported by the Dorta group largely suppressed the competing isomerization.²⁹ This catalyst gave the desired

Scheme 4^a

^a Reagents and conditions: (a) see Table 2; (b) DDQ, CH_2Cl_2 , pH 7 buffer, $0\text{ }^{\circ}\text{C}$, 87%; (c) TBAF, THF, $60\text{ }^{\circ}\text{C}$, 85%; (d) see ref 30.

Table 2. Catalyst Optimization for the RCM of Substrate **34**^a

No.	Catalyst (mol %)	T ($^{\circ}\text{C}$)	Yield (%)	38:39 ^b
1	6 (20)	80	56	63:37 ^c
2	6 (20)	120	54	79:21 ^d
3	41 (2 \times 20)	80	35	nd
4	42 (20)	60	dimer	
5	43 (10)	120	76–78	95:5 ^{d,e}

^a All reactions were performed in toluene; $c = 1\text{--}2\text{ mM}$. ^b Determined by ^1H NMR. ^c In the presence of $\text{Cy}_3\text{P}=\text{O}$ (20 mol %). ^d The catalyst was added over 2 h via syringe pump. ^e In the presence of tetrafluoro- q -quinone (2 \times mol % of catalyst loading); nd = not determined.

product **38** in appreciable yields, and only very small amounts of the 11-membered congener **39** were detected.

The further elaboration of **38** was straightforward, comprising the deprotection of the dimethoxybenzyl (DMP) group with buffered DDQ followed by removal of the stereodirecting silyl substituent with TBAF (Scheme 4). The resulting product **40** intercepts our previous total synthesis of lactimidomycin and can be elaborated into this target in five high yielding operations.³⁰

In summary, we have shown that the strategic positioning of a silyl group allows *E,Z*-configured macrocyclic 1,3-dienes to be formed in good to excellent yields with unprecedented levels of regio- and stereocontrol. The $\text{R}_3\text{Si}-$ moiety functions as a protecting group for the internal alkene and, at the same time, plays an active role as the key stereodirecting substituent. A successful application to the total synthesis of the cell migration inhibitor lactimidomycin underscores the relevance of this methodology, which also deserves a conceptual remark. One of the greatest triumphs of ruthenium-based metathesis catalysts in general stems from the fact that they allow alkenes to be selectively activated in the presence of almost any polar substituent. This exquisite profile largely obviated the need for protecting group chemistry and hence strongly improved the “economy of steps” of contemporary synthesis.³¹ Yet, the current study seems to imply that an ever increasing catalyst activity may actually render “protecting groups for alkenes”

advantageous or even mandatory in certain cases, for which only few choices are known.³² It will be interesting to see whether further studies support or disprove this notion.³³

ASSOCIATED CONTENT

S Supporting Information. Experimental section, additional control experiments, preparation of the substrates, and NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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