



NIH PUBLIC ACCESS

Author Manuscript

J Am Chem Soc. Author manuscript; available in PMC 2014 December 18.

Published in final edited form as:

J Am Chem Soc. 2014 November 26; 136(47): 16493–16496. doi:10.1021/ja510768c.

Preparation of Macrocyclic Z-Enoates and (*E,Z*)- or (*Z,E*)-Dienoates through Catalytic Stereoselective Ring-Closing Metathesis

Hanmo Zhang[§], Elsie C. Yu[§], Sebastian Torker[§], Richard R. Schrock[‡], and Amir H. Hoveyda^{§,*}

[§]Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

[‡]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Abstract

The first examples of catalyst-controlled stereoselective macrocyclic ring-closing metathesis reactions that generate *Z*-enoates as well as (*E,Z*)- or (*Z,E*)-dienoates are disclosed. Reactions promoted by 3.0–10 mol % of a Mo-based monoaryloxide pyrrolide complex proceed to completion within 2–6 h at room temperature. The desired macrocycles are formed in 79:21 to >98:2 *Z/E* selectivity; stereoisomerically pure products can be obtained in 43–75% yield after chromatography. Utility is demonstrated by application to a concise formal synthesis of the natural product (+)-aspicilin.

Macrocyclic structures containing a carbonyl unit conjugated to one or more alkenes are present in many biologically active molecules.¹ Other than ester bond-forming reactions, Horner–Emmons-type transformations and catalytic ring-closing metathesis (RCM) are two distinct approaches that allow access to large-ring *E*-enoates. Reactions between an aldehyde and a stabilized phosphonium ylide represent a reliable way of synthesizing macrocycles; RCM, however, obviates the need for protecting group manipulations and/or oxidation state adjustments that often accompany the involvement of a carbonyl group. Macrocyclic *Z*-enoates can be obtained by reactions performed under modified Horner–Emmons conditions,² through the use of Still–Gennari-type phosphonate esters³ or by partial hydrogenation of ynoates.⁴ Catalyst-controlled *Z*-selective RCM has the potential to give macrocyclic *Z*-enoates efficiently, facilitating synthesis of molecules such as callispongolide⁵ (Scheme 1a).⁶ Further, RCM offers an attractive option for preparing macrocyclic (*E,Z*)-⁷ or (*Z,E*)-dienoates; macrolactin A⁸ is an example of a natural product

© 2014 American Chemical Society

Corresponding Author: amir.hoveyda@bc.edu.

Notes

The authors declare no competing financial interest.

Supporting Information

Experimental procedures and spectral and analytical data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

that contains such a moiety (Scheme 1b). Alternatively, the dienolate unit may be site-selectively and diastereoselectively functionalized;⁹ the case corresponding to preparation of aspicilin¹⁰ is representative (Scheme 1b). Despite the above considerations, macrocyclic RCM processes that deliver large ring enoates and/or dienolates containing a *Z*-alkene are yet to be disclosed. Here we report catalytic RCM reactions that generate such entities efficiently and stereo-selectively.

We first examined the ability of Ru, Mo, and W complexes, commonly used and/or shown to be effective in *Z*-selective macrocyclic RCM,⁶ to promote the formation of 14-membered-ring *Z*-enoate **2** (Table 1). Reaction with dichloro-Ru complex **3** was efficient (87% conv, 12 h), generating the lower energy *E* isomer selectively (5:95 *Z/E*, entry 1). Under conditions similar to those reported for RCM of unactivated dienes,^{6c} there was no detectable transformation after 12 h in the presence of 10 mol% bidentate Ru complex **4** (entry 2). With bis-alkoxide **5** (entry 3), only 42% conv was observed, presumably due to competitive catalyst deactivation/decomposition; *E*-**2** was again formed preferentially (16:84 *Z/E*).

We then turned to examining monoaryloxide pyrrolide (MAP) complexes under conditions that allow for relatively facile reaction (100 Torr, C₆H₆, 22 °C).^{6a,b} Use of W or Moalkylidenes **6** and **7a** led to minimal reaction¹¹ (entries 4 and 5, Table 1). Based on computational investigations indicating that a more electron withdrawing imido group can impart electronic stabilization of the metallacyclobutane intermediates to increase efficiency,^{6d} we probed the activity of 2-(trifluoromethyl)-phenylimido complex **7b** (entry 6). After 2 h, 24% of **2** was formed with 72:28 *Z/E* selectivity. To enhance selectivity, we opted for a more sizable aryloxide ligand according to our original stereochemical model.¹² However, use of MAP complex **8** led to complete loss of activity.

At this point, we chose to prepare and examine MAP alkylidenes **9a,b**, complexes that have not been previously utilized. This was based on the hypothesis that electronic activation imposed by the comparatively diminutive pentafluorophenylimido ligand might improve catalyst performance^{6d} while giving rise to elevated *Z* selectivity by residing opposite to the sterically demanding aryloxides in the metallacyclobutane intermediates. In the event, when **9a** was used, 60% conv to **2** was observed along with 89:11 *Z/E* selectivity (entry 8). When the aryloxide substituents were altered from 2,4,6-trimethylphenyl in **9a** to a 2,4,6-tri(isopropyl)phenyl moiety, catalyst activity disappeared entirely (entry 9). Optimization studies indicated that 3.0–5.0 mol% of the in situ-generated MAP complex **9a** is sufficient to bring about considerable conversion under 100 Torr of pressure, at ambient temperature and after 2 h (Scheme 2). Longer reaction times did not lead to further transformation.

Different macrocyclic *Z*-enoates, from 14- to 19-membered rings (**2**, **10–14**, Scheme 2), can be synthesized in 79:21–90:10 *Z/E* selectivity. As the formation of 24-membered-ring **15a** indicates, the catalytic protocol may be extended to larger macrocyclic compounds. After silica gel chromatography, pure *Z* product isomers were isolated in 43–70% yield. Ring closures are often more efficient for ring sizes larger than 15. Consistent with this trend, our efforts to obtain a 12-membered *Z*-enoate proved unsuccessful (<2% desired product). Depending on the ring size and/or the nature of the substituents, RCM of an acyclic diene precursor that contains additional functionality might result in improved or diminished

efficiency.¹³ Thus, reactions leading to 16- and 17-membered-ring products **11b** and **12b** proceeded to higher conversion and afforded the *Z*-enoates in better yield compared to **11a** and **12a**.

Attempts to promote reactions that produce different α,β -unsaturated amides led to negligible transformation (Scheme 3). The disparity between the reactions of ester and amide substrates might arise from the ability of the latter to form Mo alkylidenes that can be unreactive because of stronger chelation of the amide carbonyl with the transition metal and/or A(1,3)-strain when R = Bn or Boc.¹⁴ Moreover, unlike Boc amide substituents or unprotected indole units, the presence of a primary carbamate, such as that in the expected product **15b**, leads to substantial activity loss; this might arise from association of the Lewis basic unit with the Mo center and/or the acidity of the said substituent.

Macrocyclic dienoates of diverse ring sizes can be prepared through the use of 5.0–10 mol% of **9a** (Scheme 4). In cases involving *E*-dienoate as substrates (e.g., **16**, Scheme 4a), unlike transformations that afford *Z*-enoates, cyclizations proceed with complete control of stereoselectivity (>98:2 *Z/E*) for up to 18-membered rings. In contrast, **20** is formed in 91:9 *Z:E* selectivity. RCM with Ru complexes represented by **3** and **4** proved inefficient (e.g., <10% conv to **18** with 10 mol% complex after 12 h). With the more active Mo bis-alkoxide **5**, 20 mol% loading was required to achieve 50% and 34% conv to **18** and **19**, respectively (<10% conv with 10 mol%). In the latter cases, whereas **18** was generated with complete *Z* selectivity (similar to when **9a** was used), there was minimal preference in the case of **19** (65% *Z*). Catalytic RCM leading to isomeric (*Z,E*)-dienoates was performed with *E*-diene substrates (e.g., **21**, Scheme 4b).¹⁵ Stereoselectivity was lower in these latter systems (cf. **22**, **23** vs products in Scheme 4a), but isomerically pure macrocyclic dienoates were obtained after chromatography. Use of Ru dichloride **3** or Mo bis-alkoxide **5** did not yield any desired product. Such disparities underscore the unique ability of Mo MAP complexes to deliver the appropriate balance of longevity and reactivity.

The transformations in Scheme 5 were carried out to demonstrate utility of the approach. Conversion of **24**¹⁶ to **25** (80% yield) was followed by RCM with 10 mol% **9a** afforded stereoisomerically pure (*E,Z*)-dienoate **26** in 69% yield. Oxidative removal of the *p*-methoxybenzyl group generated **27** (91% yield), which has been converted to aspicilin.¹⁷

For cyclic (*E,Z*)-dienoates (Scheme 4a) that are 18-membered, RCM processes are completely *Z*-selective regardless of the type of Mo alkylidene used (**5** or **9a**); for 19-membered ring **20**, better *Z* selectivity is obtained with **9a**, suggesting considerable catalyst control. This is unlike cyclizations that lead to enoates (Scheme 2) or (*Z,E*)-dienoates (Scheme 4b). To gain insight regarding the above trends, we calculated (DFT) the thermodynamic stereochemical preferences for unfunctionalized cyclic alkenes (Figure 1, A),^{6b-d} cyclic enoates (B; cf. Scheme 2); cyclic dienoates with an (*E*)- α,β -unsaturated carbonyl and a (*Z*)- γ,δ -alkene (C; cf. Scheme 4a), and those that bear a (*Z*)- α,β -unsaturated enoate and an (*E*)- γ,δ -alkene (D; cf. Scheme 4b). With a sufficiently large ring, the thermodynamic preference approaches that of acyclic systems. However, while the energy difference [$G(E) - G(Z)$] for type A and C rings does not exceed ~1 kcal/mol (A' and C' , Figure 1), the *E* isomer can be significantly more stable in type B and D olefins ($G \approx 2$

kcal/mol; cf. B' and D'). For enoates and diennoates, the thermodynamic preference for the *E* isomer is reached at larger ring sizes compared to the less functionalized variants (A) for which the turning point is at about the 11-membered ring system (13–18-membered rings in B–D). With the less extensive conjugation in a macrocyclic α,β -unsaturated ester, the *E* alkenes containing more than 13 atoms become favored (B). On the contrary, preference for (*E,E*)-diennoates is reached when 18–19-membered rings are being generated (C and D, Figure 1). The G value in the case of (*Z,E*)-diennoates (D') is larger (by ~1 kcal/mol) for ring sizes above ~18 atoms [vs (*E,Z*)-diennoates in C'], consistent with the weaker drive for formation of *E* alkenes in RCM that furnish (*E,Z*)-diennoates (C) vs *Z,E* isomers (D).

These studies expand the applicability of *Z*-selective olefin metathesis to include a set of transformations that is likely to find substantial utility in chemical synthesis. Development of related cross-metathesis reactions¹⁸ and studies on the impact of the resulting *Z*-enoates and diennoates on the design of multistep routes for preparation of complex biologically active molecules^{6e,18e} are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support was provided by the NIH (GM-59426). We thank T. J. Mann and A. W. H. Speed for helpful discussions.

References

1. Review on biologically active macrocyclic compounds: Yu X, Sun D. *Molecules*. 2013; 18:6230. [PubMed: 23708234]
2. Representative reports: Williams DR, Kiryanov AA, Emde U, Clark MP, Berliner MA, Reeves JT. *Angew Chem, Int Ed*. 2003; 42:1258. Lucas BS, Gopalsamuthiram V, Burke SD. *Angew Chem, Int Ed*. 2007; 46:769.
3. Examples: Forsyth CJ, Ahmed F, Cink RD, Lee CS. *J Am Chem Soc*. 1998; 120:5597. Smith AB III, Minbirole KP, Verhoest PR, Schelhaas M. *J Am Chem Soc*. 2001; 123:10942. [PubMed: 11686698] O'Neil GW, Phillips AJ. *J Am Chem Soc*. 2006; 128:5340. [PubMed: 16620095]
4. Selected cases: Evans DA, Fitch DM, Smith TE, Cee VJ. *J Am Chem Soc*. 2000; 122:10033. Wender PA, Hegde SG, Hubbard RD, Zhang L. *J Am Chem Soc*. 2002; 124:4956. [PubMed: 11982349] Nelson SG, Cheung WS, Kassick AJ, Hilfiker MA. *J Am Chem Soc*. 2002; 124:13654. [PubMed: 12431077]
5. Pham CD, Hartmann R, Böhler P, Stork B, Wesselborg S, Lin W, Lai D, Proksch P. *Org Lett*. 2014; 16:266. [PubMed: 24329175]
6. Reports on *Z*-selective macrocyclic RCM and applications to natural product synthesis: Yu M, Wang C, Kyle AF, Jakubec P, Dixon DJ, Schrock RR, Hoveyda AH. *Nature*. 2011; 479:88. [PubMed: 22051677] Wang C, Yu M, Kyle AF, Jakubec P, Dixon DJ, Schrock RR, Hoveyda AH. *Chem—Eur J*. 2013; 19:2726. [PubMed: 23345004] Rosebrugh LE, Herbert MB, Marx VM, Keitz BK, Grubbs RH. *J Am Chem Soc*. 2013; 135:1276. [PubMed: 23317178] Wang C, Haeffner F, Schrock RR, Hoveyda AH. *Angew Chem, Int Ed*. 2013; 52:1939. Yu M, Schrock RR, Hoveyda AH. *Angew Chem, Int Ed*. 2014.1002/anie.201409120.
7. Synthesis of acyclic (*E,Z*)-diennoates by Still–Gennari conditions: Chemler SR, Coffey DS, Roush WR. *Tetrahedron Lett*. 1999; 40:1269.

8. Report on synthesis of macrolactin A (does not involve macrocyclic RCM): Smith AB III, Ott GR. *J Am Chem Soc.* 1996; 118:13095. For selected other natural products containing the same (Z,E)-enoate unit, see: Shin Y, Fournier JH, Fukui Y, Brückner AM, Curran DP. *Angew Chem, Int Ed.* 2004; 43:4634. Bishara A, Rudi A, Aknin M, Neumann D, Ben-Califa N, Kashman Y. *Tetrahedron Lett.* 2008; 49:4355.
9. For instance: den Hartog T, Harutyunyan SR, Font D, Minnaard AJ, Feringa BL. *Angew Chem, Int Ed.* 2008; 47:398. Uraguchi D, Yoshioka K, Ueki Y, Ooi T. *J Am Chem Soc.* 2012; 134:19370. [PubMed: 23145913] Lee, K-s; Wu, H.; Haeffner, F.; Hoveyda, AH. *Organometallics.* 2012; 31:7823. [PubMed: 23264716] Luo Y, Roy ID, Madec AGE, Lam HW. *Angew Chem, Int Ed.* 2014; 53:4186.
10. Selected disclosures on total synthesis of asplicilin (none involve macrocyclic RCM): Enders D, Prokopenko OF. *Liebigs Ann.* 1995:1185. Kobayashi Y, Nakano M, Kumar GB, Kishihara K. *J Org Chem.* 1998; 63:7505. [PubMed: 11672404] Dixon DJ, Foster AC, Ley SV. *Org Lett.* 2000; 2:123. [PubMed: 10814262] Gandhi VR. *Tetrahedron.* 2013; 69:6507.
11. The less reactive W MAP complexes typically require longer reaction times than Mo alkylidenes.
12. (a) Ibrahim I, Yu M, Schrock RR, Hoveyda AH. *J Am Chem Soc.* 2009; 131:3844. [PubMed: 19249833] (b) Meek SJ, O'Brien RV, Llaveria J, Schrock RR, Hoveyda AH. *Nature.* 2011; 471:461. [PubMed: 21430774]
13. An early study regarding the influence of substituents on the facility of a macrocyclic RCM reaction promoted by a Mo alkylidene: Xu Z, Johannes CW, Houry AF, La DS, Cogan DA, Hofilena GE, Hoveyda AH. *J Am Chem Soc.* 1997; 119:10302.
14. Amide complexes derived from Mo complexes and their structure/activity relationships: Sattely ES, Cortez GA, Moebius DC, Schrock RR, Hoveyda AH. *J Am Chem Soc.* 2005; 127:8526. [PubMed: 15941288] Townsend EM, Kilyanek SM, Schrock RR, Müller P, Smith SJ, Hoveyda AH. *Organometallics.* 2013; 32:4612. [PubMed: 24082360]
15. With 5.0 mol% **9a** after 2 h, ~70% conv was observed, but since **21** and **22** are not easily separable, conditions that lead to higher conv were used.
16. See the SI for preparation of alkene **24**.
17. Quinkert G, Heim N, Glenneberg J, Billhardt UM, Autze V, Bats JW, Dürner G. *Angew Chem, Int Ed Engl.* 1987; 26:362.
18. Representative Z-selective cross-metathesis reactions: (a) Ref 12b. Kiesewetter ET, O'Brien RV, Yu EC, Meek SJ, Schrock RR, Hoveyda AH. *J Am Chem Soc.* 2013; 135:6026. [PubMed: 23586708] Mann TJ, Speed AWH, Schrock RR, Hoveyda AH. *Angew Chem, Int Ed.* 2013; 52:8395. (d) Ref 6e Speed AWH, Mann TJ, O'Brien RV, Schrock RR, Hoveyda AH. *J Am Chem Soc.* 2014.10.1021/ja509973r Herbert MB, Marx VM, Pederson RL, Grubbs RH. *Angew Chem, Int Ed.* 2013; 52:310. Quigley BL, Grubbs RH. *Chem Sci.* 2014; 5:501.

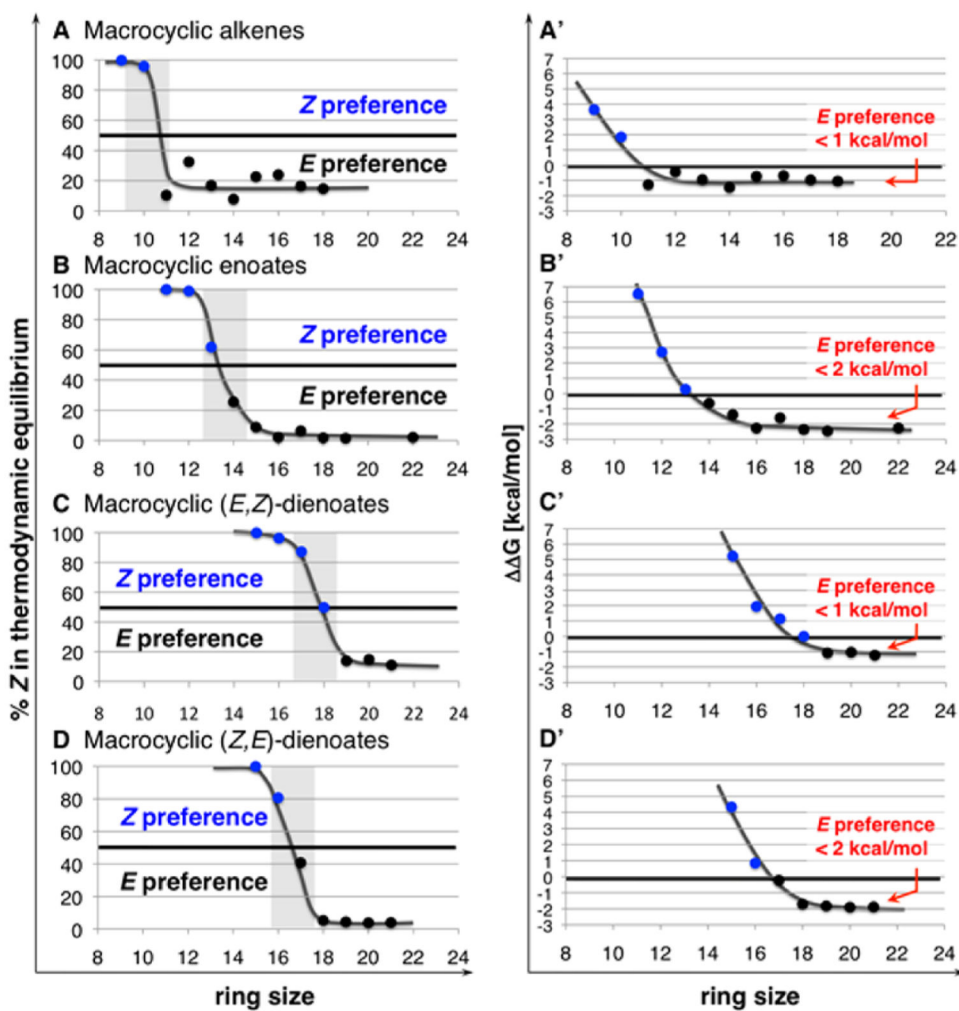
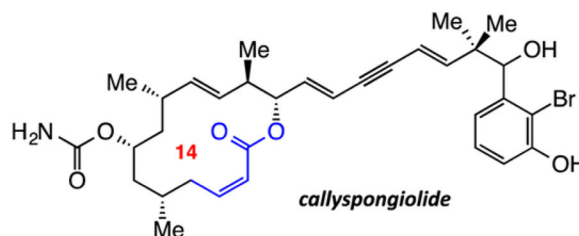
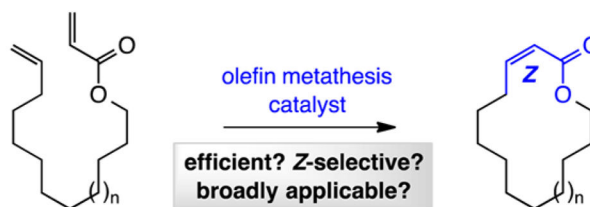
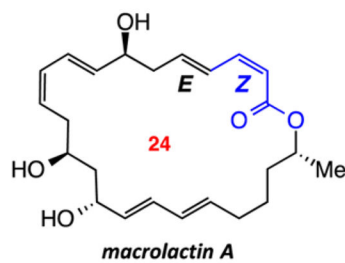
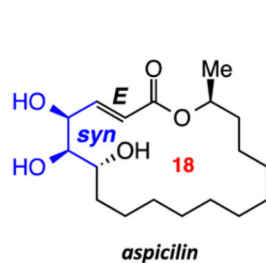
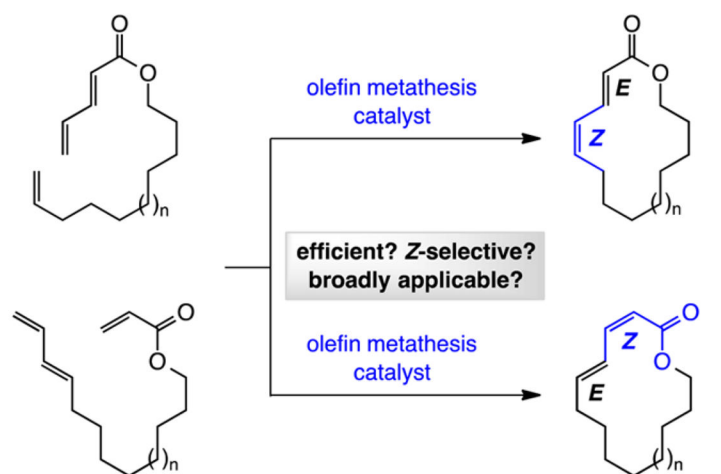
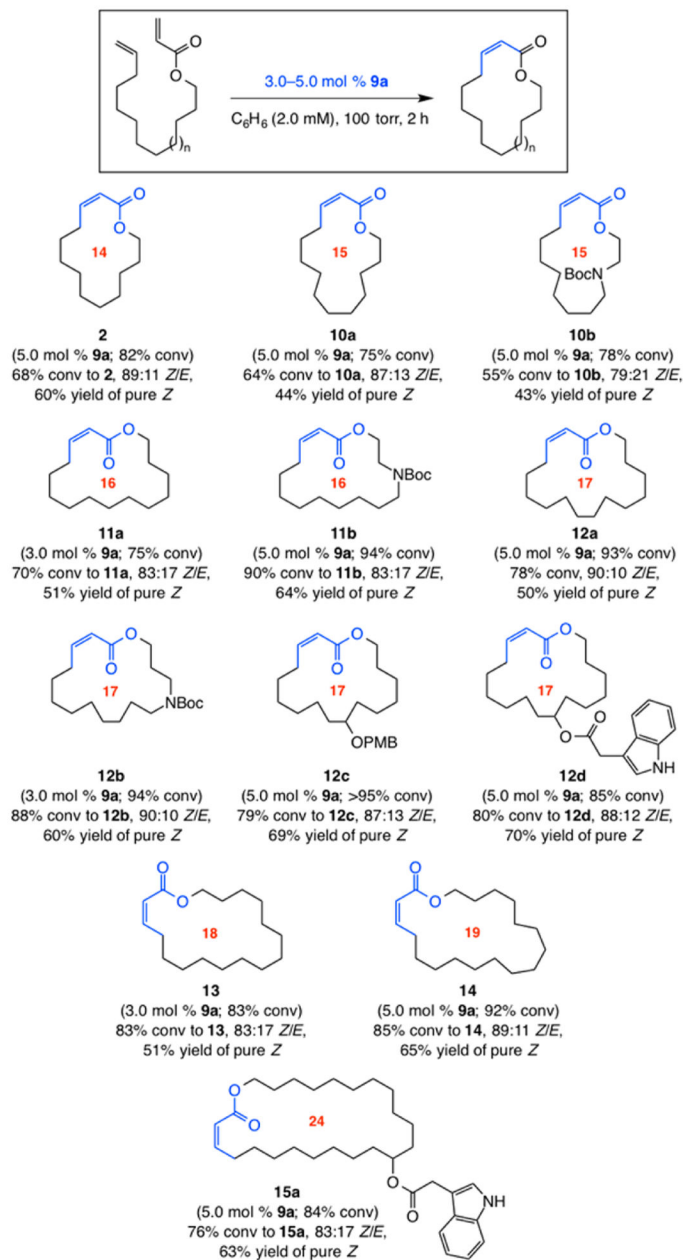


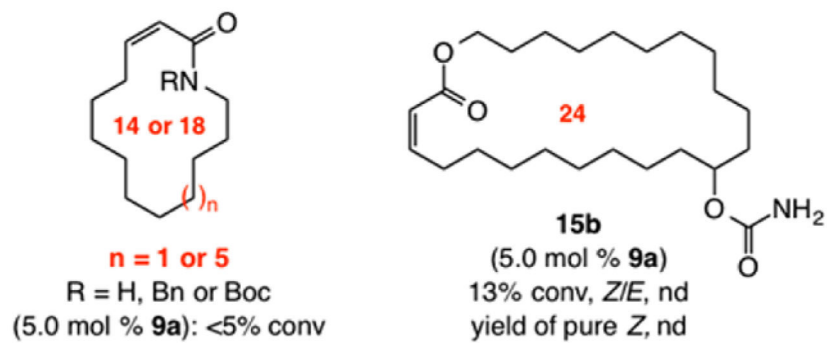
Figure 1. Variations in the thermodynamic preferences of different unsaturated macrocyclic alkenes. See the SI for details of calculations.

a. Macrocyclic Z-enoates:**b. Macrocyclic (E,Z)- & (Z,E)-dienoates:**

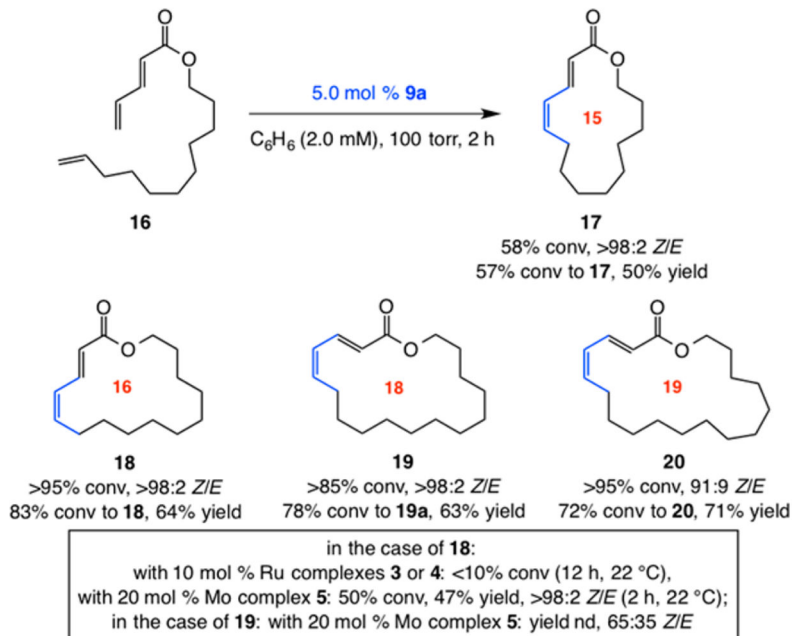
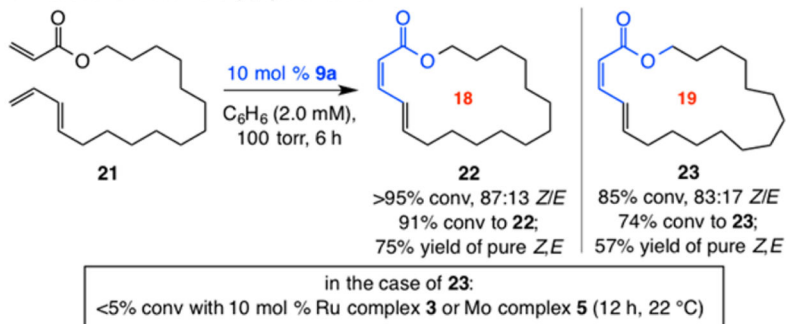
Scheme 1.
Synthesis of Macrocyclic Enoates by Z-Selective RCM

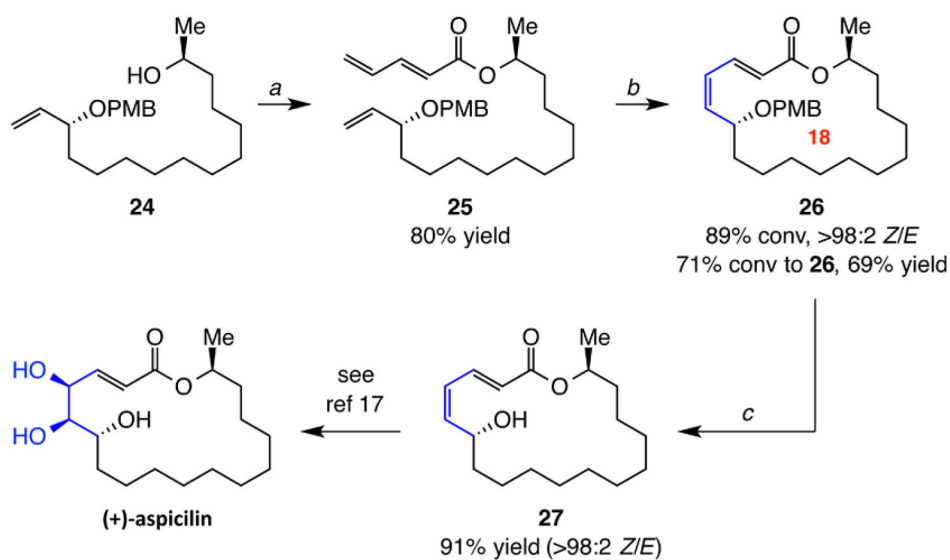
**Scheme 2. Z-Selective Macrocyclic Enoate RCM^a**

^aReactions leading to **2**, **10a,b**, and **11a** performed at 1.0 mM. Conv = formation of desired macrocycle. See the SI for details.

**Scheme 3^a**

^a See the SI for details. nd = not determined.

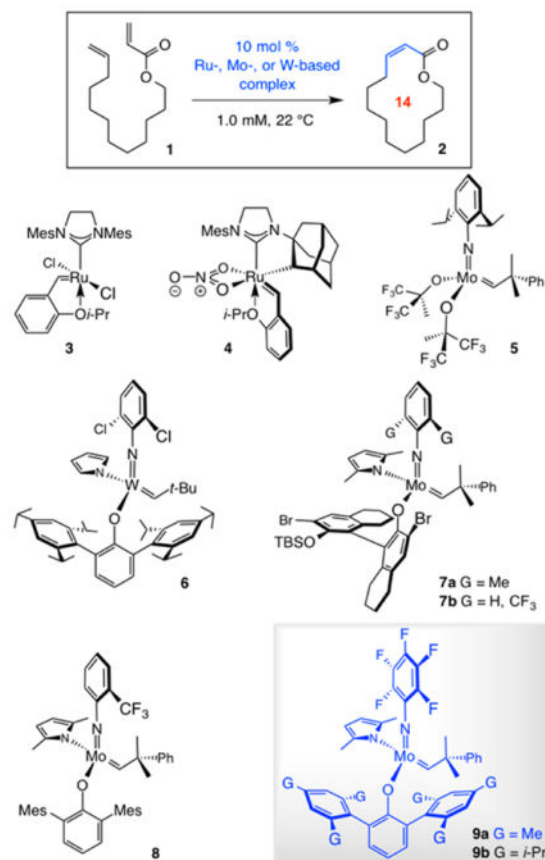
a. Reactions that afford (*E,Z*)-dienoates:b. Reactions that afford (*Z,E*)-dienoates:Scheme 4. *Z*-Selective Formation of Macrocyclic Dienoates by RCM^a^aConv = formation of the desired macrocycle. See the SI for details.



Scheme 5. Application to Formal Synthesis of (+)-Aspicilin^a

^aConditions: (a) pentadienoic acid, pivaloyl chloride, DMAP, Et₃N. (b) 10 mol% **9a**, C₆H₆, 22 °C, 100 Torr, 6 h. (c) DDQ, CH₂Cl₂/H₂O, 0 °C, 1 h. Conv = formation of desired macrocycle. See the SI for details.

Table 1

Screening of Ru, Mo, and W Complexes^a

entry	complex	condition	time (h); conv (%) ^b ; conv to 2 (%) ^b	Z/E ^b
1	3	ambient; CH ₂ Cl ₂	12; 92; 87	5:95 ^c
2	4	100 torr; Cl(CH ₂) ₂ Cl	12; <5; na	nd
3	5	ambient; C ₆ H ₆	12; 61; 42	16:84 ^c
4	6	100 torr; C ₆ H ₆	12; <5; na	nd
5	7a	100 torr; C ₆ H ₆	2; <10; na	nd
6	7b	100 torr; C ₆ H ₆	2; 30; 24	72:28
7	8	100 torr; C ₆ H ₆	2; <10; na	nd
8	9a	100 torr; C ₆ H ₆	2; 79; 60	89:11
9	9b	100 torr; C ₆ H ₆	2; <5; na	nd

^aReactions were performed under N₂ atmosphere.^bConversion (total consumption of **1**) and Z:E ratios (±2%) were determined by analysis of ¹H NMR spectra of unpurified mixtures.

^cProduct mixture contained ca. 50% of the dimeric macrocycle. See the Supporting Information (SI) for details. Mes = 2,4,6-(Me)₃C₆H₂; na = not applicable; nd = not determined.