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Catalyst-Controlled Stereoselective Olefin Metathesis as a Principal Strategy in Multi-Step Synthesis Design. A Concise Route to (+)-Neopeltolide**

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Abstract

Mo-, W- and Ru-based complexes that control the stereochemical outcome of olefin metathesis reactions have been recently introduced. However, the complementary nature of these systems through their combined use in multistep complex molecule synthesis has not been illustrated. Here, we disclose a concise diastereo- and enantioselective route that furnishes the anti-proliferative natural product neopeltolide. Catalytic transformations are employed to address every stereochemical issue. Among the featured processes are an enantioselective ring-opening/cross-metathesis promoted by a Mo monopyrrolide aryloxide (MAP) complex and a macrocyclic ring-closing metathesis affording a trisubstituted alkene catalyzed by a Mo bis-aryloxide species. Furthermore, Z-selective cross-metathesis reactions, facilitated by Mo and Ru complexes, have been employed in stereoselective synthesis of the acyclic dienyl moiety of the target molecule.

Keywords

catalysis; leucascandrolide A; olefin metathesis; enantioselective synthesis; neopeltolide; synthesis

Catalytic olefin metathesis (OM) has had a strong impact on the art of complex molecule synthesis,^[1] an influence all the more remarkable because it has largely been despite the lack of related catalyst-controlled stereoselective transformations. For years, the possibility of preferential formation of one stereoisomer depended exclusively on thermodynamic preferences that are seldom predictable and virtually impossible to alter. Since 2009, Mo, W

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and Ru catalysts have been introduced that facilitate Z-selective ring-opening/cross-metathesis (ROCM),^[2] cross-metathesis (CM)^[3] or macrocyclic ring-closing metathesis (MRCM);^[4] in some instances, reactions can be enantioselective too.^[2a–b,c–d,g] The utility of individual Z-selective OM processes have been demonstrated in a limited number of cases.^[3a,4a–c] There is however no record of a set of multi-step sequences that are principally based on the recently introduced stereoselective OM processes, illustrating their strengths and weakness or the nuances of any symbiotic relationships.

We now report an enantioselective synthesis of anti-proliferative agent neopeltolide,^[5] a natural product with the same linear appendage as that of cytotoxic leucascandrolide A^[6,7] (Scheme 1). The successful route features OM reactions promoted by Mo and W monoaryloxide pyrrolide (MAP), Mo bis-aryloxide perfluoroimido as well as catechothiolate Ru complexes; it illustrates the complementary nature of different catalyst architectures,^[8] indicating that catalysts developed for attaining high Z selectivity may also be critical for achieving high efficiency.^[9]

The overall plan and questions regarding the central catalytic transformations are presented in Scheme 2. To access the macrolactone, we envisioned a succession of catalytic MRCM (**ii**→**i**, Scheme 2a) followed by diastereoselective reduction of the resulting trisubstituted alkene by catalytic hydrogenation (peripheral mode of addition).^[10] Former studies attest to the positive impact of MRCM versus macrolactonization and its attendant protecting group manipulations and oxidation state adjustments.^[5] Nonetheless, in former approaches to neopeltolide formation of a trisubstituted alkene by RCM involved disubstituted olefins and required the use of 20–30 mol % of a Ru catalyst at elevated temperatures (80–100 °C).^[5g, 11] It was further demonstrated that formation of the alkene in **i** proceeds with complete Z selectivity due to energetic preferences of the macrocycle, and that subsequent hydrogenation can be exceptionally stereoselective.^[5g, 11] For us, therefore, the main challenge was to identify a catalyst that is capable of delivering the requisite olefin more efficiently (i.e., **ii**→**i**).

Diene **ii** would be synthesized by the coupling of enantiomerically enriched carboxylic acid **iii** and secondary alcohol **vi** (Scheme 2a). We would access the necessary segments through catalytic enantioselective reactions, with the heterocyclic fragment **iv** being generated by ROCM with unsaturated oxabicycle **v**.

Preparation of the unsaturated side chain was designed to explore the scope of the state-of-the-art in Z-selective CM. We decided that it would be strategically advantageous to form the more hindered oxazole-substituted alkene first (cf. **viii**, Scheme 2b); this would lower the odds of the Z olefin's isomerization while the less sterically demanding alkene of the side chain is being formed (**vi** → **vii**). Direct CM of vinyloxazole (**ix**) and allylcarbamate could deliver **viii** efficiently and stereoselectively. Another plan would entail Z-selective CM with vinyl(pinacolato)boron [vinyl-B(pin)] to afford **xi**, followed by catalytic cross-coupling (CC) with iodooxazole **x**. An additional question was the identity of the most effective cross partner for the second stereoselective CM, one that could provide access to the Z- α,β -unsaturated ester (i.e., the nature of R in **vi** in Scheme 2b).

We first examined the feasibility of the route for the macrocyclic fragment (Scheme 2a). The enantioselective boronate conjugate addition to α,β -unsaturated amide **1**, accessible in one step from commercially available materials, was catalyzed by the chiral N-heterocyclic carbene (NHC) derived from imidazolium salt **2** (Scheme 3).^[12,13] Subsequent oxidation afforded β -hydroxy amide **3** in 86% overall yield and 95:5 enantiomeric ratio (e.r.). Conversion to the β,γ -unsaturated ketone and directed Tishchenko-type reduction in the presence of SmI_2 ^[14] generated the *anti* mono-benzoyl product in >99:1 diastereomeric ratio (d.r.). Methyl ether formation and removal of the ester unit afforded alcohol **4** in 53% overall yield (four steps; >99:1 d.r., 95:5 e.r.). The above sequence was performed in significant scale to furnish more than one gram of β -hydroxy ester **3**. It merits note that the NHC-catalyzed synthesis of β -hydroxy carbonyl **3** is a more efficient substitute to diastereoselective aldol protocols involving a chiral auxiliary, and subsequent conversion to the desired amide.^[15] Moreover, as far as we are aware, catalytic enantioselective acetate aldol processes with Weinreb amide-type reactants remain undisclosed.

Preparation of the pyran moiety commenced with an enantioselective ROCM involving oxabicyclic alkene **5**^[16] and commercially available *n*-butyl vinyl ether in the presence of 0.6 mol % Mo MAP complex **6a** (Scheme 3a). Within 10 minutes at ambient temperature, one gram of **5** was converted to pyran **7** in 88% yield (1.2 g) and 99:1 e.r. as a single alkene isomer (>99:1 *Z:E*; Scheme 3a). Hydrolysis and oxidation of the aldehyde delivered carboxylic acid **8** in 86% overall yield. Although we have previously shown that the ROCM reaction can be promoted by a chiral Ru carbene,^[2d] use of Mo alkylidene **6a** led to a more efficient process (60–75% yield, 90:10–95:5 e.r. with 5.0 mol % carbene in 24 h).

The union of alcohol **4** and acid **8** delivered diene **9**, which was isolated in 88% yield in the stereoisomerically pure form (>98:2 d.r. and e.r.).^[17] Macrocyclic alkene **11** was obtained in 89% yield by treatment of **9** with 8.0 mol % Mo bisaryloxide **10** (22 °C, 3.0 h).^[4c] The superior performance of the perfluoroimido alkylidene is underscored by a comparative analysis with selected other catalyst constructs (Scheme 3b). With 10 mol % hexafluoro-*t*-butoxide Mo alkylidene **13**^[18] there was 65% conversion (64% yield). MAP complexes (e.g., **14a**)^[19] and Ru carbenes (cf. **15a–b**)^[20] were less effective. When carbenes **15a–b** were used, the MRCM had to be performed at 80 °C for the trisubstituted olefin to be isolated in 49–54% yield (55–65% conv.). Diastereoselective hydrogenation of the trisubstituted olefin **11** proceeded with concomitant removal of the benzyl ether to give saturated alcohol **12** in 92% yield and 98:2 d.r.^[5g,11]

Identifying a short and stereoselective route to the linear diene fragment was next. We initially considered direct *Z*-selective CM of allylic carbamate **16** and the corresponding heterocyclic alkene, but found that such a pathway is low yielding and moderately *Z*-selective (Scheme 4). The inefficiency arises from facile homocoupling of **16** (vs. CM), probably leading to higher ethylene concentration and the somewhat unstable methylenide species (despite the use of vacuum). What's more, the latter complex can readily react with the kinetically generated alkene isomer to cause *Z*-to-*E* isomerization. We did not consider utilizing excess vinyloxazole, a substrate that would have to be prepared in three steps (vs. the simpler **16**), as a viable option.

We then explored the feasibility of a CM/CC sequence (Scheme 5). Nearly two grams (86% yield) of stereoisomerically pure *Z*-alkenyl-B(pin) **19** was prepared through stereoselective CM involving vinyl-B(pin)^[3b] and the less hindered allylcarbamate **16** (vs. vinyloxazole) in the presence of 3.0 mol % Mo MAP complex **14b**. Phosphine-Pd-catalyzed CC of **19** with K₃PO₄ and heterocyclic iodide **20** delivered *Z*-disubstituted alkene **21** in 82% yield (>98:2 *Z:E*).^[21] Use of excess vinyl-B(pin) has several advantages. Formation of the B(pin)-substituted complex is almost certainly faster than or at least competitive with the alkylidene derived from **16**; this is likely because the Lewis acidic boron can better stabilize electron density at the carbon of the Mo=C unit.^[22] In addition, the B(pin)-substituted alkylidene is more prone to react with the less hindered allylcarbamate than undergo reaction with another sizeable vinyl-B(pin) molecule. Alcohol **21** was converted to terminal alkene **22** in two steps (Scheme 5), setting the stage for installment of the second (less congested) *Z* alkene.

A direct approach to forming the second *cis* olefin of the side chain fragment would involve a *Z*-selective CM with an α,β -unsaturated carbonyl compound, a hitherto unknown process. Preliminary studies indicated that CM with **22** and *t*-butylacrylate is inefficient ($\leq 30\%$ conv. with 5.0 mol % Mo MAP complexes). In these latter transformations the enoate was used in excess (3.0 equiv.) to discourage facile homocoupling of the more valuable terminal alkene. Such slow rates probably arise from diminished reactivity of the acrylate-derived alkylidene, which is electronically stabilized and suffers from internal chelation of the carbonyl group^[23] with the transition metal.

As an alternative, we examined the ability of W MAP complex **23** to promote *Z*-selective CM of **22** with allyl-B(pin).^[3b] Unlike formation of the more hindered oxazole-substituted alkene, where a less active W alkylidene delivered <10% conversion, here, with a more accessible *Z* alkene, a more moderately active catalyst would minimize post-OM isomerization and is consequently preferable. In the event, use of 10 mol % **23** led to 60% conversion after three hours; longer reaction times did not lead to further conversion. Alcohol **24** was obtained after oxidation in 51% overall yield and 90:10 *Z:E* selectivity (Scheme 6).

In pursuit of a more selective and higher yielding transformation, we considered accessing the desired allylic alcohol directly by *Z*-selective CM. However, this type of OM reaction that was without precedent. To explore such a possibility, we turned to Ru catechthiolate complexes^[2e-f] and found that with Ru carbene **25a** and commercially available *Z*-2-butene-1,4-diol, *Z* allylic alcohol **24** can be obtained in 55% yield (vs. 51% yield with **23**) and with improved stereoselectivity (97:3 vs. 91:9 *Z:E*). Mechanistic studies suggested that diminishing electron density at the anionic sulfur ligand sites would increase the longevity of the catalytically active species. We therefore performed the CM with dichloro-Ru complex **25b** (10 mol %), allowing us to isolate **24** in 70% yield and 98:2 *Z:E* selectivity. The higher selectivity attained through Ru complex **25b** is critical since separation of the alkene isomers of **24** is challenging (this is also the case with the derived carboxylic acid). We did not observe any isomerization at the first alkene site.

What remained was the completion of the total synthesis. Oxidation of the primary alcohol afforded carboxylic acid **26** in 75% overall yield (Scheme 6).^[24] Coupling of the

macrocyclic and linear diene fragments **12** and **26**, respectively, furnished (+)-neopeltolide in 74% yield.

We demonstrate that, together with other catalytic processes, a blend of Mo-, W- and Ru-catalyzed enantio- and/or *Z*-selective OM reactions constitute an effective general strategy in organic synthesis. The total synthesis, where every problem of stereoselectivity was resolved by a catalytic process or a combination thereof,^[25] thus stands as the shortest disclosed for neopeltolide (28 steps including the preparation of oxabicyclic substrate **5**); the longest linear sequence is 11 steps (**5**→**12**→neopeltolide), proceeding in 20.9% overall yield (vs. 13 steps and 9.5% overall yield for the most efficient route reported previously^[5g]).

Supplementary Material

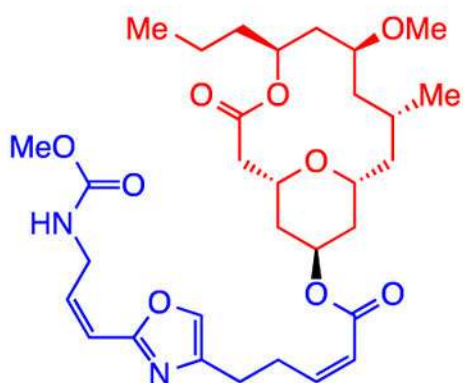
Refer to Web version on PubMed Central for supplementary material.

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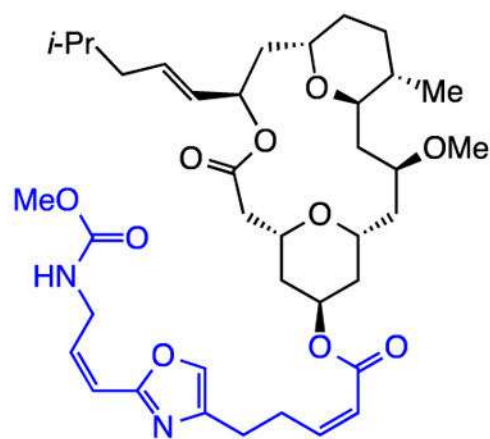
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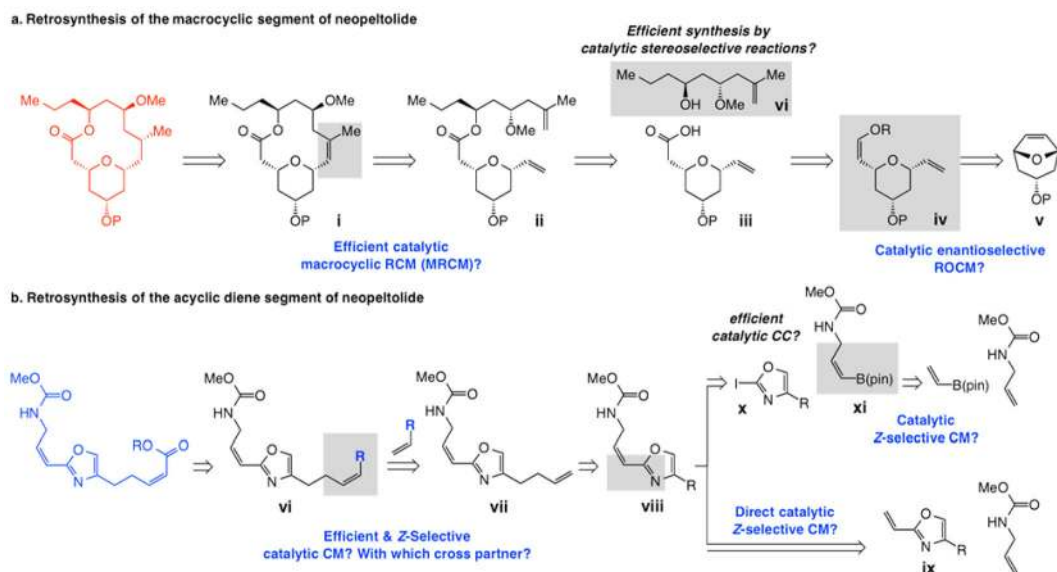
neopeltolide
(anti-proliferative)



leucascandrolide A
(cytotoxic)

Scheme 1.

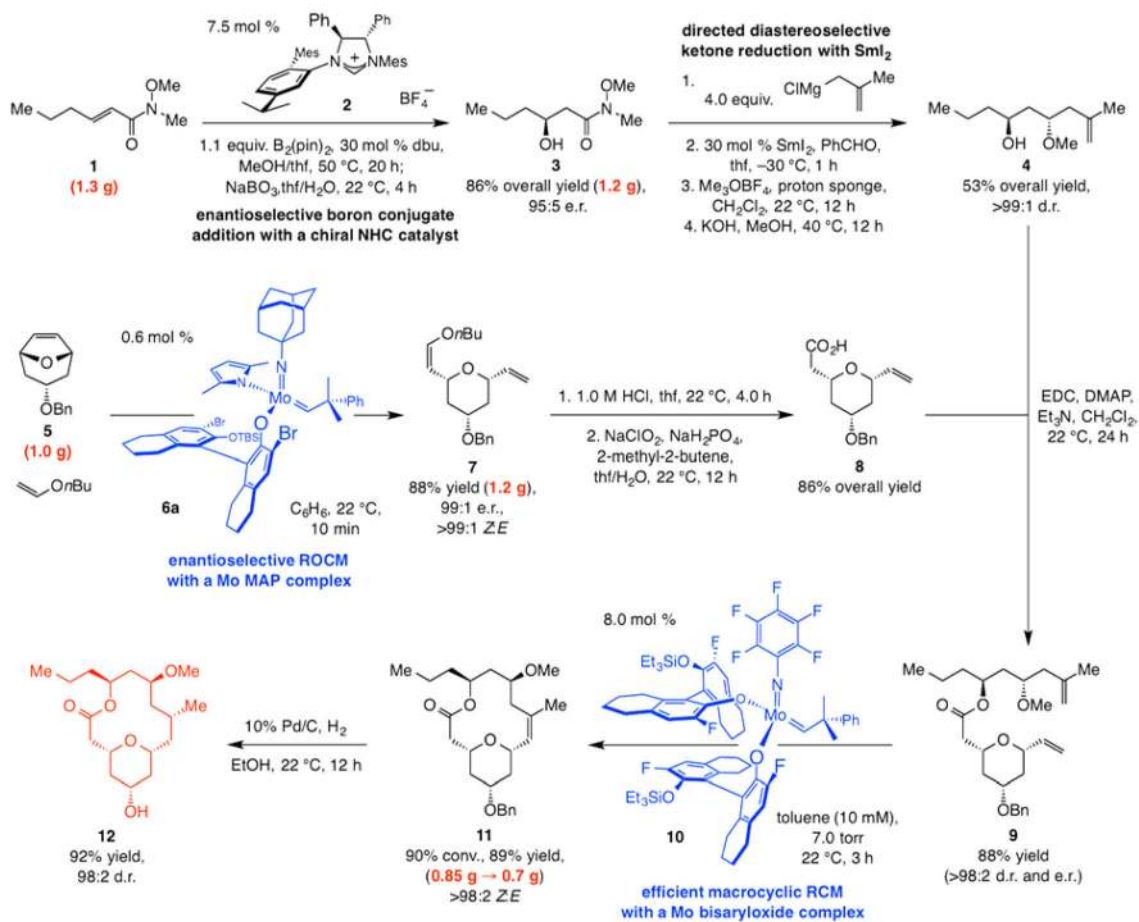
Naturally occurring anti-proliferative agent neopeltolide and potent cytotoxic leucascandrolide A.



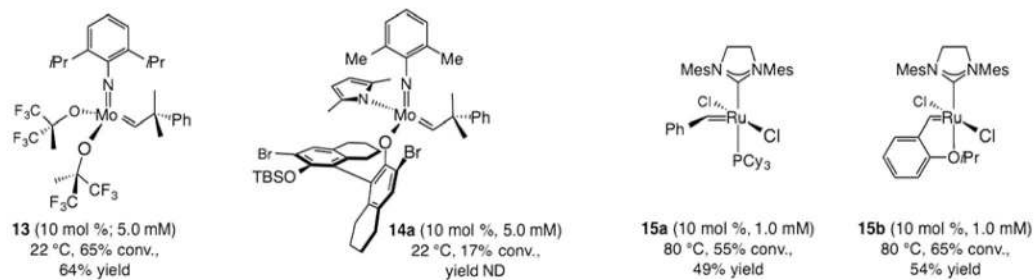
Scheme 2.

Retrosynthesis of neopeltolide (and leucascandrolide A side chain) and related issues arising from implementation of various catalytic olefin metathesis reactions; RCM = ring-closing metathesis, ROCM = ring-opening/cross-metathesis, CM = cross-metathesis, pin = pinacolato, CC = cross-coupling.

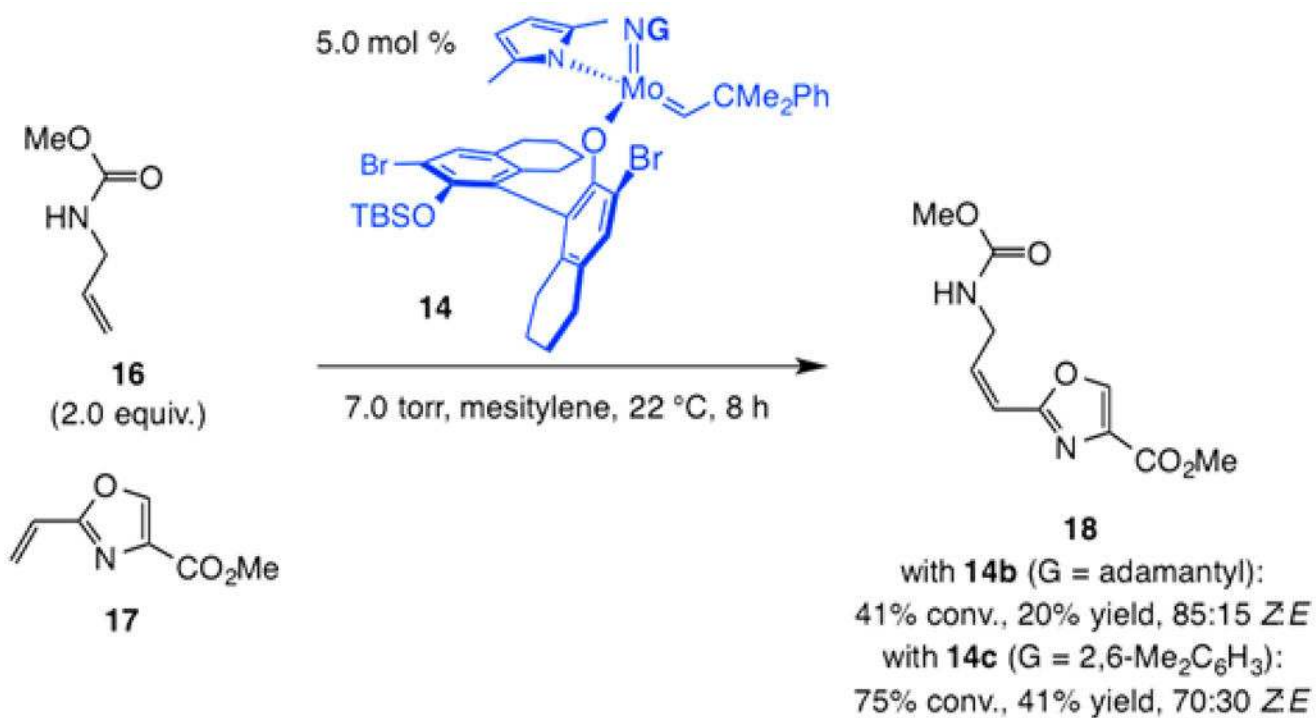
a. Synthesis of the macrocyclic segment of neopeltolide



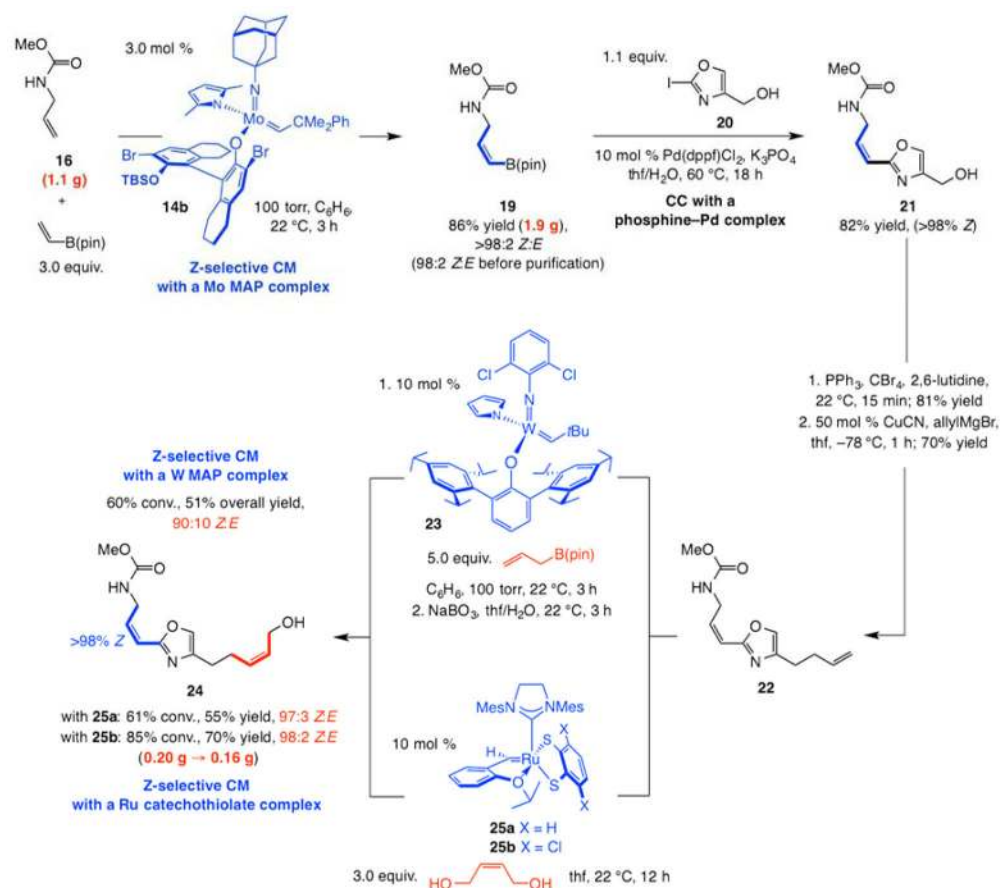
b. Effectiveness of other olefin metathesis catalysts for the macrocyclic RCM leading to macrocyclic alkene 11

**Scheme 3.**

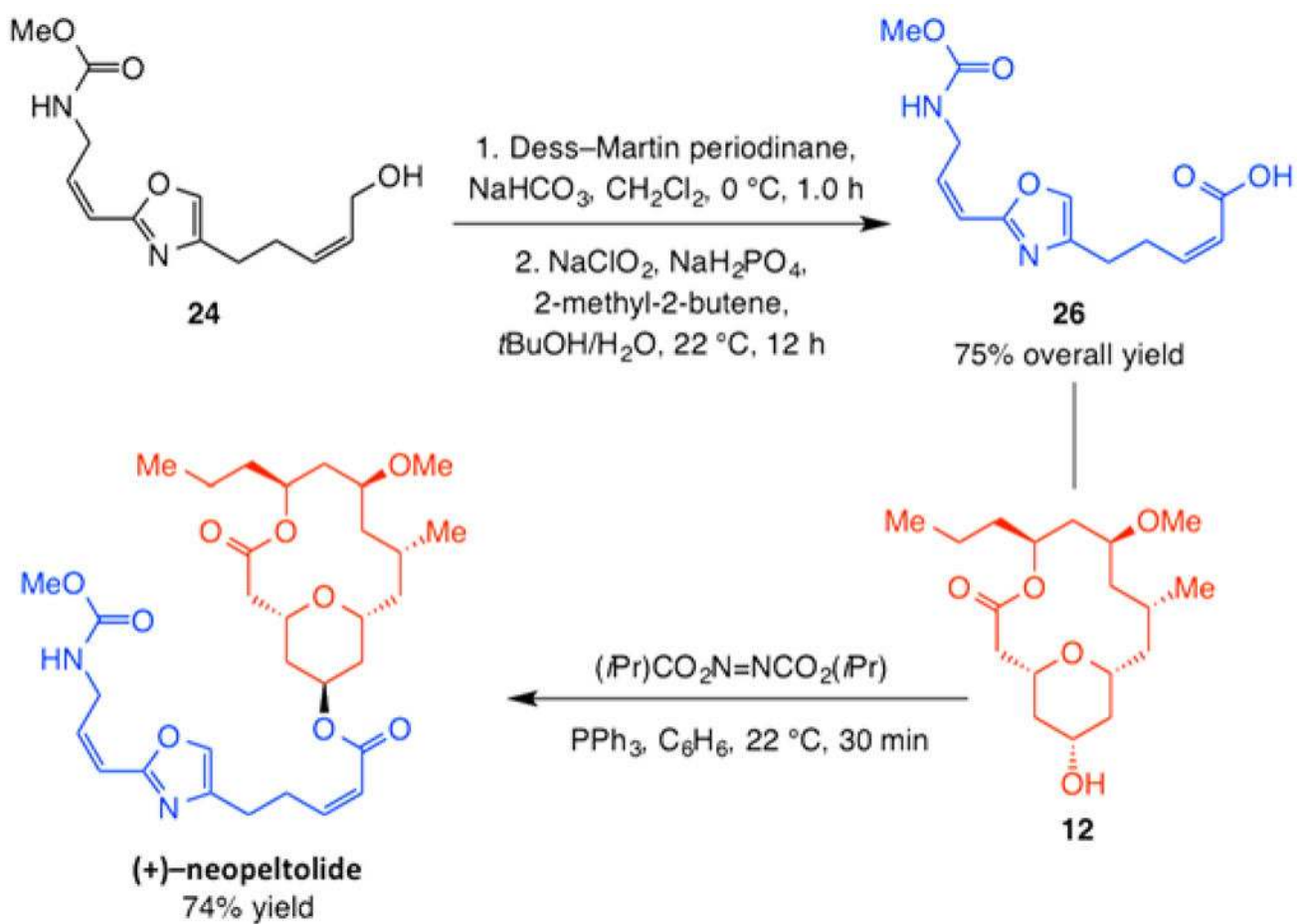
Enantioselective synthesis of the macrocyclic fragment of neopeltolide and the effectiveness of some of the more commonly used Mo and Ru complexes to promote the macrocyclic RCM. Mes = 2,4,6-(Me)₃-C₆H₂. ND = not determined.



Scheme 4.
Representative attempts regarding Z-selective CM of allylcarbamate **15** and a vinyloxazole **16**.

**Scheme 5.**

Stereoselective synthesis of the side chain of neopeltolide and leucascandrolide A carried out through the use of Mo-, W- and Ru-catalyzed Z-selective CM as well as a Pd-catalyzed CC process.

**Scheme 6.**

The final steps of diastereo- and enantioselective synthesis of (+)-neopeltolide.