Olefin Metathesis

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

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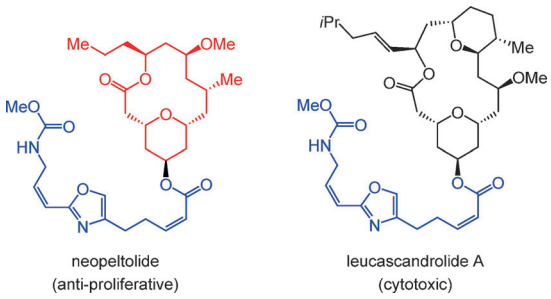
Dedicated to L. T. Scott on the occasion of his 70th birthday

Abstract: *Molybdenum-, tungsten-, and ruthenium-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. A concise diastereo- and enantioselective route that furnishes the anti-proliferative natural product neopeltolide is now disclosed. Catalytic transformations are employed to address every stereochemical issue. Among the featured processes are an enantioselective ring-opening/cross-metathesis promoted by a Mo monoaryloxide pyrrolide (MAP) complex and a macrocyclic ring-closing metathesis that affords a trisubstituted alkene and is catalyzed by a Mo bis(aryloxide) species. Furthermore, Z-selective cross-metathesis reactions, facilitated by Mo and Ru complexes, have been employed in the stereoselective synthesis of the acyclic dienyl moiety of the target molecule.*

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 achieved 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, molybdenum, tungsten, and ruthenium 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–d,g] The utility of individual *Z*-selective OM processes has been demonstrated in a limited number of cases.[3a,4a–c] There is, however, no record of a set of multistep sequences that are principally based on the recently introduced stereoselective OM processes, illustrating their strengths and weaknesses 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 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 those developed for attaining high *Z* selectivity may also be critical for achieving high efficiency.[9]



Scheme 1. Naturally occurring anti-proliferative agent neopeltolide and potent cytotoxic leucascandrolide A.

The overall plan and questions regarding the central 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 generation of the alkene in **i** proceeds with complete *Z* selectivity owing to energetic preferences of the macrocycle, and that subsequent

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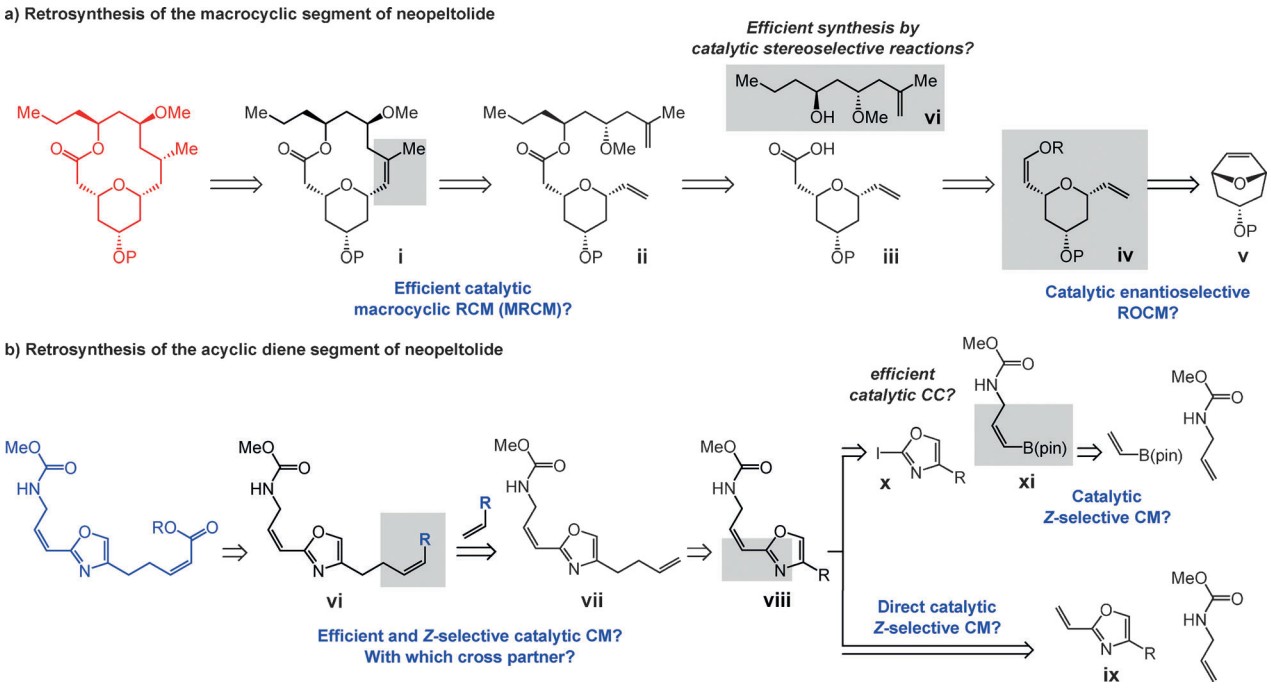


Scheme 2. Retrosynthesis of neopeltolide (and the leucascandrolide A side chain) and related issues arising from implementation of various catalytic olefin metathesis reactions. pin = pinacolato.

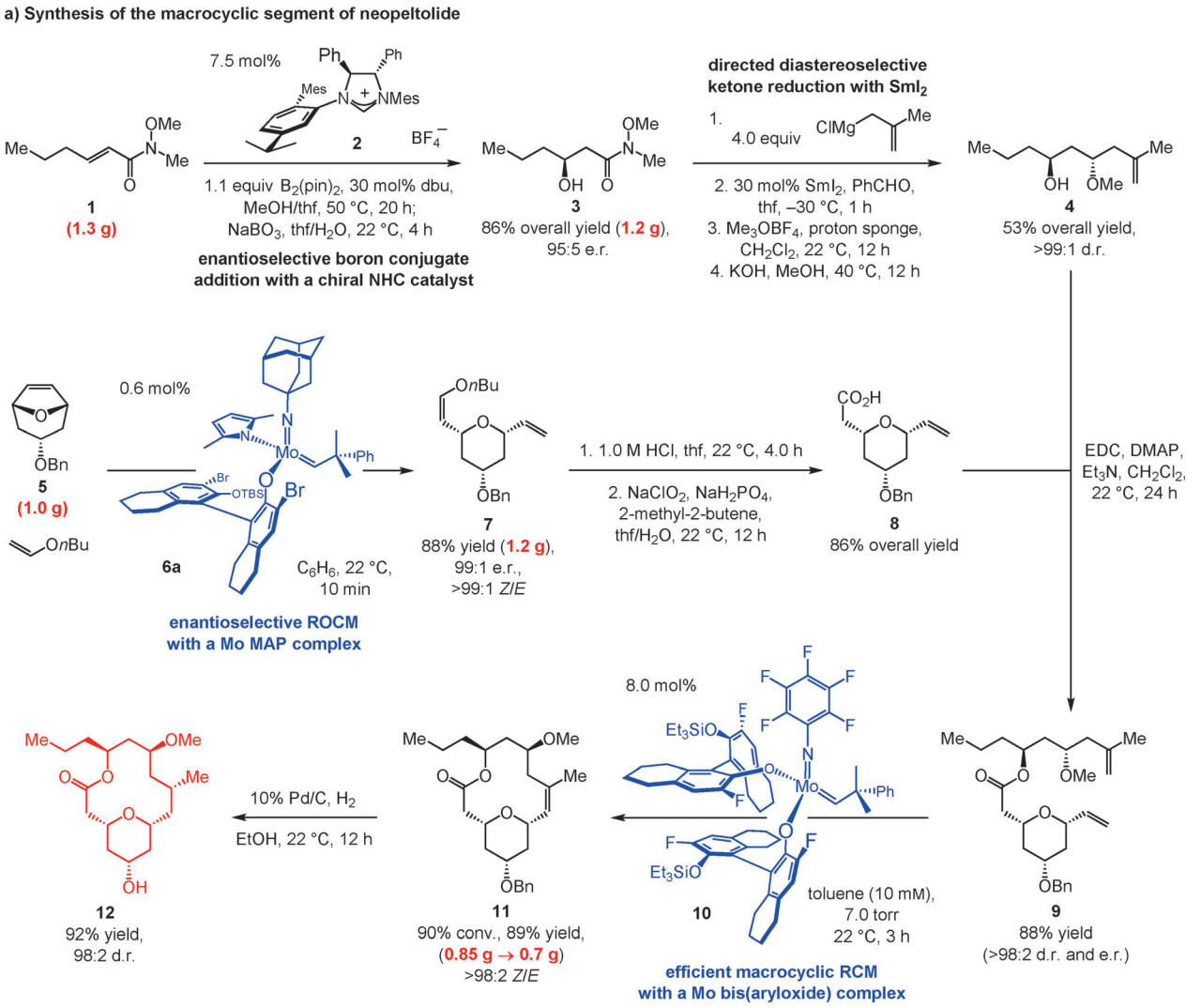
hydrogenation can be exceptionally stereoselective.[5g,11] For us, therefore, the main challenge was to identify a catalyst that is capable of delivering the requisite olefin more efficiently (i.e., **ii**→**i**). Diene **ii** would be synthesized by the coupling of enantiomerically enriched carboxylic 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 *Z* olefin isomerization while the less sterically demanding alkene of the side chain is being formed (**vii**→**vi**). Direct CM of vinyloxazole **ix** and an allyl carbamate 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*-configured α,β-unsaturated ester (i.e., the nature of R in **vi**; 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**, which is accessible in one step from commercially available materials, was catalyzed by the chiral N-heterocyclic carbene (NHC) derived from imidazolinium 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 into the β,γ-unsaturated ketone and directed Tishchenko-type reduction in the presence of SmI_2[14] generated the *anti* monobenzoyl 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 compound **3** is a more efficient substitute to diastereoselective aldol reactions involving a chiral auxiliary and subsequent conversion into 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% of Mo MAP complex **6a** (Scheme 3a). Within ten minutes at ambient temperature, one gram of **5** was converted into 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 complex,[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% of carbene in 24 h).

The union of alcohol **4** and acid **8** gave diene **9**, which was isolated in 88% yield in 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% of Mo bis(aryloxide) **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

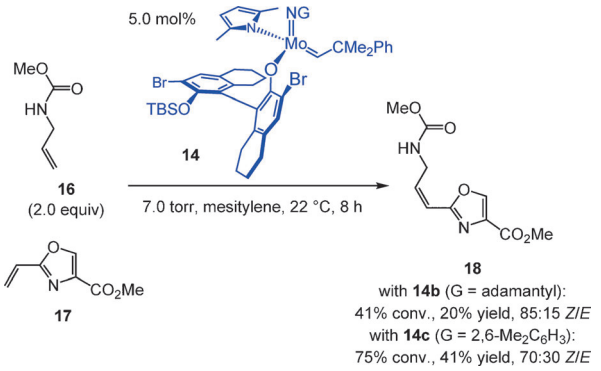


Scheme 3. Enantioselective synthesis of the macrocyclic fragment of neopeltolide and the effectiveness of some of the more commonly used Mo and Ru complexes to promote the macrocyclic RCM. Bn = benzyl, Cy = cyclohexyl, dbu = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, Mes = 2,4,6-$(Me)_3C_6H_2$, ND = not determined, TBS = *tert*-butyldimethylsilyl.

10 mol% of hexafluoro-*tert*-butoxide Mo alkylidene **13**,[18] there was 65% conversion (64% yield). MAP complexes (e.g., **14a**)[19] and Ru carbenes (e.g., **15a**,**b**)[20] were less effective. When carbenes **15a** or **15b** were used, the MRCM reaction 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]

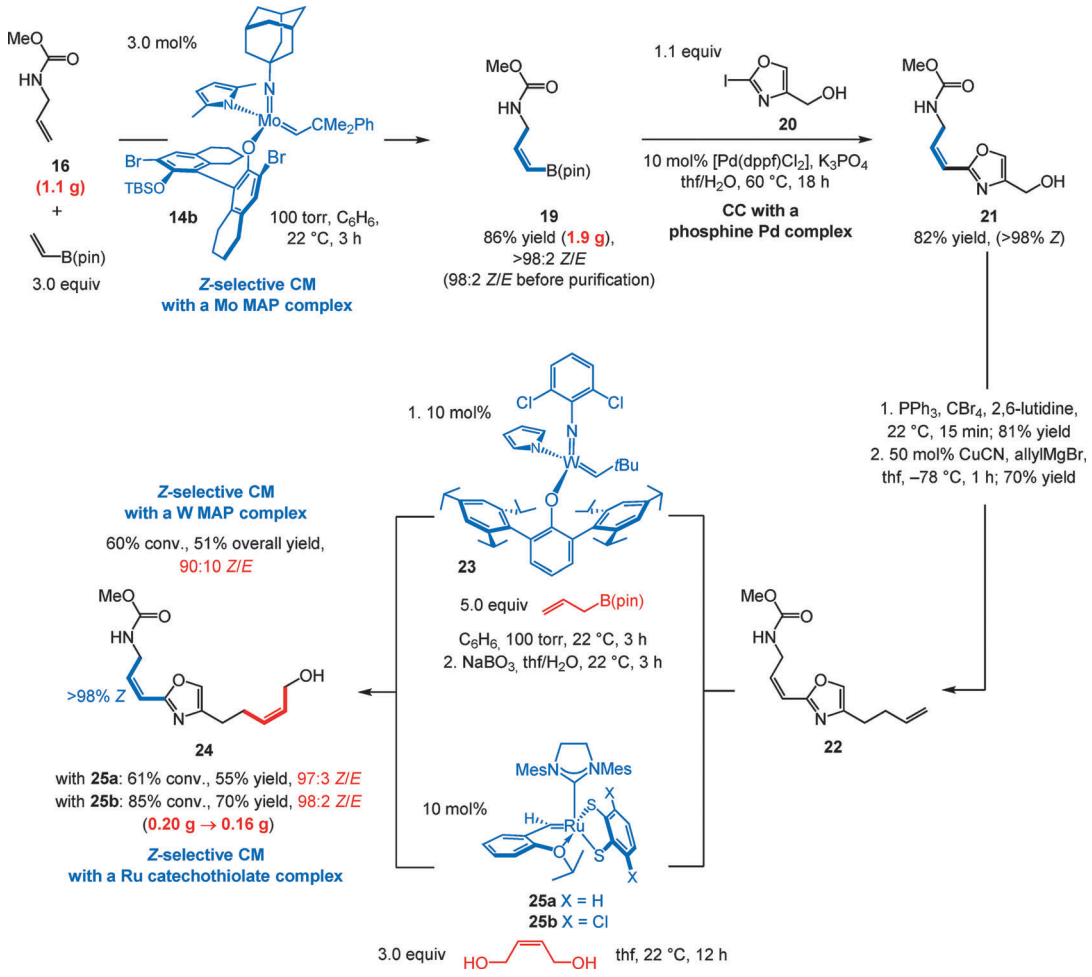
Next, a short and stereoselective route to the linear diene fragment was to be identified. We initially considered direct *Z*-selective CM of allylic carbamate **16** and the corresponding

heterocyclic alkene, but found that such a pathway was low yielding and moderately *Z*-selective (Scheme 4). The inefficiency arises from facile homocoupling of **16** (vs. CM), probably leading to a higher ethylene concentration and the somewhat unstable methylidene species (despite the use of vacuum). Moreover, the latter complex can readily react with the kinetically generated alkene isomer to cause *Z* to *E* isomerization. We did not consider utilizing an excess amount of vinyloxazole, a substrate that would have to be prepared in three steps (vs. the simpler **16**), as a viable option.



Scheme 4. Representative attempts towards the *Z*-selective CM reaction of allyl carbamate **15** and vinyloxazole **16**.

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 allyl carbamate **16** (vs. vinyloxazole) in the presence of 3.0 mol% of Mo MAP complex **14b**. CC of **19** with K_3PO_4 and heterocyclic iodide **20** catalyzed by a phosphine Pd complex delivered *Z*-disubstituted alkene **21** in 82% yield (>98:2 *Z*/*E*).[21] The use of an excess amount of vinyl–B(pin) has several advantages. Formation of the B(pin)-substituted complex is almost certainly faster than or at least competitive with formation of the alkylidene derived from **16**; this is likely because the Lewis acidic boron center 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 allyl carbamate than to undergo reaction with another sizeable vinyl–B(pin) molecule. Alcohol **21** was converted into terminal alkene **22** in two steps

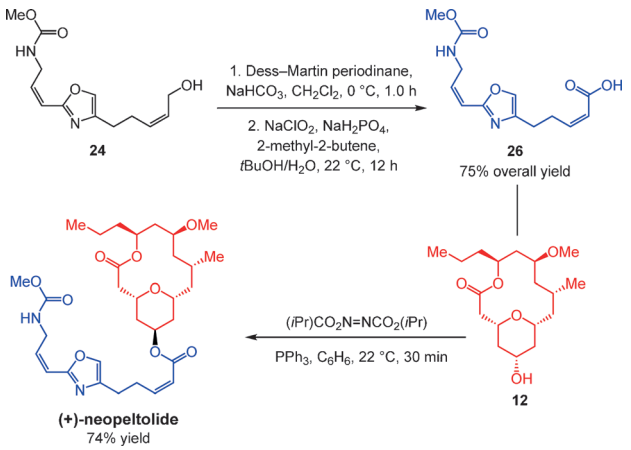


Scheme 5. Stereoselective synthesis of the side chain of neopeltolide and leucascandrolide A carried out through the use of Mo-, W-, and Ru-catalyzed *Z*-selective CM as well as a Pd-catalyzed CC processes. dppf = diphenylphosphanylferrocene.

(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 *tert*-butyl acrylate is inefficient (≤30% conv. with 5.0 mol% of 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 the *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 catalyst delivered <10% conversion, here, with a more accessible *Z* alkene, a moderately active catalyst would minimize post-OM isomerization and is consequently preferable. In the event, the use of 10 mol% of **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).



Scheme 6. The final steps of the diastereo- and enantioselective synthesis of (+)-neopeltolide.

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 was without precedent. To explore such a possibility, we turned to Ru catechothiolate complexes[2e–f] and found that with **25a** and commercially available *Z*-2-butene-1,4-diol, *Z*-configured 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 the electron density at the anionic sulfur sites would increase the longevity of the catalytically active species. We therefore performed the CM with dichloro-substituted 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 as 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 allylic carbamate 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** furnished (+)-neopeltolide in 74% yield.

We have demonstrated that, together with other catalytic processes, a blend of Mo-, W-, and Ru-catalyzed enantio- and/or *Z*-selective OM reactions constitutes an effective general strategy in organic synthesis. The route presented here, 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 long (**5**→**12**→neopeltolide) and proceeds in 20.9% overall yield (vs. 13 steps and 9.5% overall yield for the most efficient route reported previously).[5g]

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