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An enyne metathesis approach to the synthesis of the 1,3-diene system of mycothiazole

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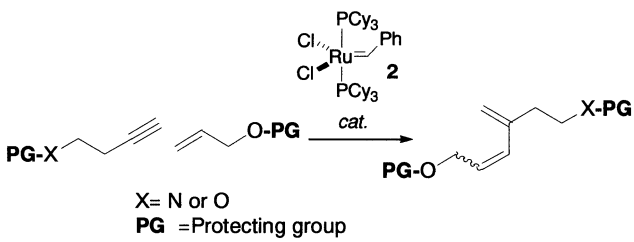
Abstract—The 1,3-diene fragment present in mycothiazole was synthesized by the use of a key cross-enyne metathesis from accessible starting materials.

With the advent of the well-defined catalysts developed independently by the groups of Grubbs and Schrock, olefin metathesis has acquired increased significance in organic synthesis.[1] Although numerous examples exist of the ring-closing metathesis of dienes (RCM), little is known about RCM involving both alkynes and alkenes at the same time. Since the first reported enyne metathesis,[2] most effort has been focused on the intramolecular version of this reaction and which has become established as a very useful tool for the synthesis of cycloalkenes.[3] Mori and Kinoshita succeeded in the total synthesis of (−)-stemoamide, using Grubbs' ruthenium–carbene catalyst, where an enyne metathesis reaction was a key step.[4] This reaction has been used in the synthesis of cyclic β-lactams,[5] alkenyl-substituted cyclic enol ethers,[6] constrained α-amino acids,[7] medium-sized ring compounds,[8] tetrahydroisoquinolines,[9] cyclic siloxanes,[10] perhydroindenes,[11] and, very recently, for the synthesis of the AB ring system of the manzamine alkaloids.[12] Recent developments in intramolecular enyne metathesis also include reactions in tandem.[13]

Intermolecular-enyne metathesis (cross-enyne metathesis) is a unique reaction[14] and has been developed using ethylene gas as the alkene.[15] This methodology has been used in the synthesis of chlorin–diene building blocks.[16] However, a few examples can be found in the literature where this approach has been used with other types of alkene.[17]

In this respect, metathesis of an alkyne and an alkene can lead to many olefins, dienes and polymers because three kinds of metathesis occur at the same time: intermolecular alkyne, intermolecular alkene and intermolecular enyne metatheses. Furthermore, the formation of E/Z mixtures in the final alkene is a major problem that has yet to be solved. For this reason, it is important to optimize the conditions of the reaction in order to minimize the formation of mixtures. In spite of these drawbacks, this approach has found an elegant application in the synthesis of two natural products, α-triticene and bulnesol.[18]

In the search for new bioactive lead structures, compounds of marine origin have proven to be a rich and varied source of new structural classes of secondary metabolites, many of which have very interesting pharmacological properties. Mycothiazole (**1**) was isolated by Crews et al. in 1988[19] from the Indo-Pacific sponge *Spongia mycofijiensis* collected from Vanuatu. This compound showed in vitro anthelmintic activity as well as selective activity against lung cancer cells in the NCI in vitro 60-cell line panel.[20] In the recently reported



Scheme 1. An enyne metathesis approach for the synthesis of 1,3-dienes.

Keywords: mycothiazole; enyne metathesis.

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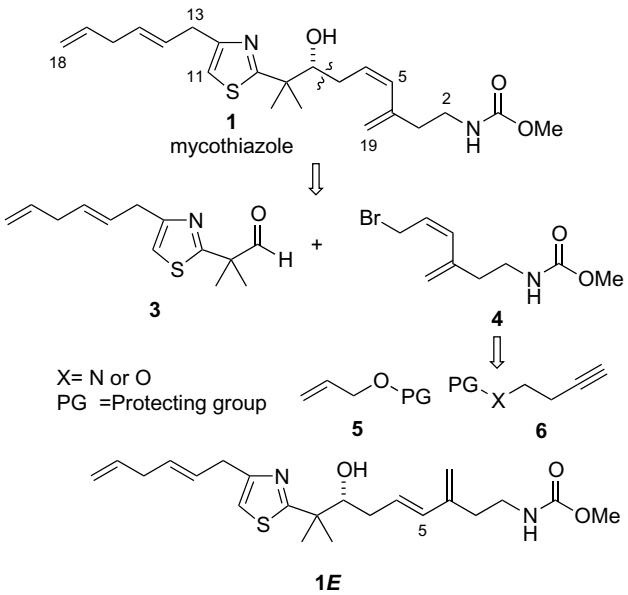
asymmetric total synthesis of **1**,[21] the conjugated *exo*- and *Z*-configured diene was constructed by a standard Stille coupling of a 1-substituted vinylstannane and a vinyl-iodine bearing the 2,4-disubtituted thiazole ring.

Here, we would like to report studies that illustrate the use of the intermolecular cross-enyne metathesis (see Scheme 1) as a method to build-up the conjugated diene present in mycothiazole. Our planned synthesis of **1** and some derivatives, which will allow us to perform SAR studies, is based on a convergent approach that combines the 1,3-diene **4** and the 1,4-diene-thiazole **3** (see Scheme 2), which can be obtained as in the previously reported synthesis of **1**. Compound **4**, which carries a fragment of the 'right arm' of mycothiazole, can be easily obtained by an intermolecular enyne cross metathesis between protected alkene **5** and alkyne **6**. This procedure could be suitable for the preparation of multigram quantities because of the easy accessibility of alkenes and alkynes in the first step of the synthesis. In addition, we will be able to access 5*E*-mycothiazole (**1*E***) and to evaluate the effect of the *E*/*Z* diene system in the bioactivity of mycothiazole.



Scheme 2. Retrosynthetic analysis of mycothiazole.

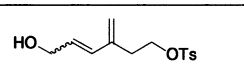
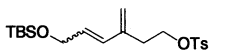
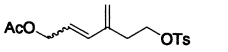
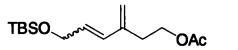
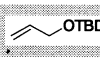
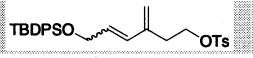
In order to optimize the key enyne metathesis, which allows us to construct the 1,3-diene present in **4**, we studied changes in the type of protecting group, concentration, solvent, time of reaction, amount of catalyst and the presence of nitrogen or oxygen in alkyne **6**. For our purposes, the use of Grubbs' catalyst, bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (**2**), seemed to be particularly well suited owing to its exceptional resistance to poisoning by polar molecules.

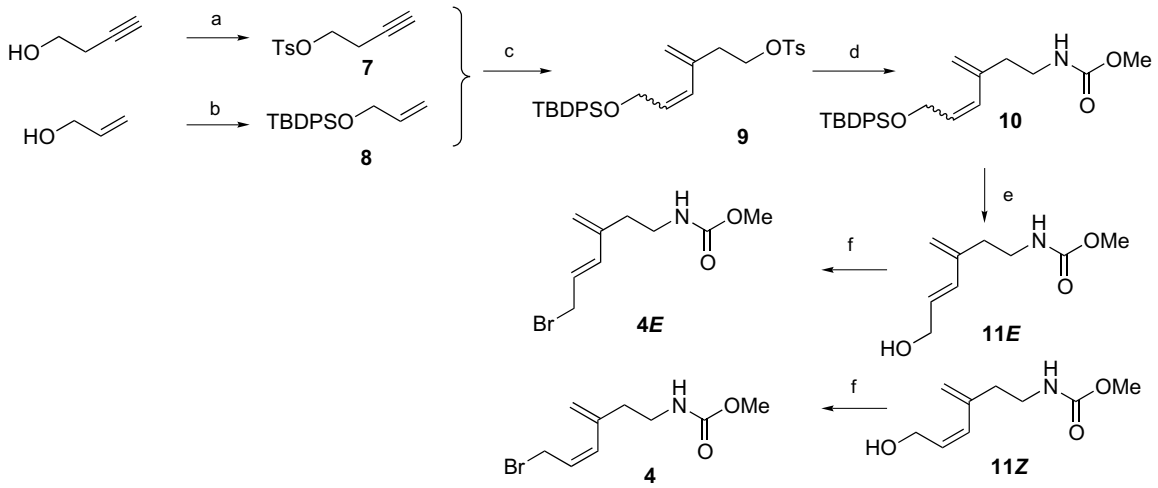
We began by using protected homopropargylic amines,[22] which were reacted with allylic alcohols in either their protected or non-protected form. Reaction of alkynes bearing monoprotected[23] amines with allyloxy-*tert*-butyldimethylsilane in the presence of 10% of ruthenium catalyst gave the expected 1,3-dienes in very poor yields and without *E*/*Z* stereoselectivity. The use of an increased temperature did not give any enyne metathesis product. Better yields were obtained using toluene as the solvent instead of methylene chloride, by carrying out the reaction at room temperature, and employing an alkyne concentration of 0.2 M.[24]

Given these poor results, we decided to employ an alkyne based on a protected homopropargylic alcohol. It was envisaged that this system could be converted, after deprotection, into the desired amine.

The presence of the protecting group in the alkene was crucial given that the 1,3-diene was not formed when the homopropargyl tosylate was reacted with the unprotected allylic alcohol. This fact can be explained in terms of a possible chelation process that results in a decrease in the reaction rate and the destruction of the catalytic system.[25] The protection of the allylic alcohol resulted in a 30% yield of the enyne metathesis product, which was further improved when the reaction was carried out in methylene chloride at room temperature for 5 h. Under the same conditions the homopropar-

Table 1. Intermolecular enyne metatheses with protected homopropargylic alcohols

Entry	*Alkyne*	*[Alkyne]*	*Alkene*	*Conditions*	*1,3-dienes*	*Yield%*	*E:Z*
a		0.2 M		CH_2Cl_2, rt, 24 h **2** cat. 10%		0	-
b	"	0.1 M		$PhCH_3$, rt, 5 h **2** cat. 10%		30	1.0:1.0
c	"	0.2 M	"	CH_2Cl_2, rt, 5 h **2** cat. 10%	"	80	1.0:1.0
d	"	0.1 M		CH_2Cl_2, rt, 5 h **2** cat. 10%		15	1.0:1.0
e		0.2 M		CH_2Cl_2, rt, 5 h **2** cat. 10%		80	1.1:1.0
f		**0.2 M**		**CH_2Cl_2, rt, 5 h** **2 cat. 10%**		**95**	**1.1:1.0**
g	"	0.2 M	"	CH_2Cl_2, rt, 5 h **2** cat. 8%	"	65	1.1:1.0
h	"	0.2 M	"	CH_2Cl_2, rt, 12 h **2** cat. 10%	"	60	1.1:1.0



Scheme 3. Synthesis of **4**. *Reagents and conditions*: (a) TsCl, CH_2Cl_2, Et_3N, 0°C, 85%; (b) ClTBDPS, DMF, Et_3N, rt, 97%; (c) CH_2Cl_2, rt, 10% **2**, 5 h; then $Pb(OAc)_4$, 12 h, 94%. (d) i. NaN_3, DMF, rt, then 50°C, 4 h; ii. Ph_3P, THF, H_2O; iii. ClCOOMe, Et_3N, 0°C then rt, 4 h, 67% (three steps); (e) i. TBAF, THF, 55°C, 2 h; ii. SiO_2–$AgNO_3$ impregnated chromatographic separation, 73%; (f) CBr_4, Ph_3P, CH_2Cl_2, 0.3 h, 82%.

gylic acetate (see entry a) gave a similar yield. The best yield in the enyne metathesis was obtained when the allylic alcohol was protected as its diphenyl-*tert*-butylsilanoxyl derivative rather than the *tert*-butyldimethylsilyl compound. In this case an increase in the yield to 95% was achieved (see Table 1, entry f).

We next turned our attention to the synthesis of the diene segment **4**, which was started by the preparation of multigram quantities of compounds **7** and **8** (see Scheme 3). The enyne cross-metathesis was carried out under the conditions already described in entry f and gave the aforementioned *E*/*Z* diene mixture **9** in a 1.1:1 ratio. Displacement of the resulting tosylates with NaN_3 provided the corresponding mixture of azides, which was reduced under mild conditions with Ph_3P/THF/H_2O and then converted into a mixture of methoxycarbamates **10** by treatment of the amines with ClCOOMe (67% yield after three steps).[26] After deprotection of the TBDPS group with TBAF in THF, the resulting mixture of allylic alcohols **11*E*** and **11*Z*** was easily separated using SiO_2 impregnated with $AgNO_3$.[27] Subsequent treatment of **11*E*** and **11*Z*** with Ph_3P and CBr_4 resulted in the expected bromides **4*E*** and **4**, respectively.[28] The successful isolation of these two compounds fulfilled the goal of this paper.

In conclusion, we have developed a concise approach to the diene core of mycothiazole by a key enyne cross metathesis from an easily accessible alkene and alkyne. This method gave the 1,3-dienes **4*E*** and **4** in a high yield. The synthetic bromides will be used for the total synthesis of the natural and the unnatural compounds **1** and **1*E***, respectively, and this process is currently underway.

Acknowledgements

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23. In the literature there are very few cases using the amines monoprotected as carbamates or sulfonamides. In these cases the enyne metathesis proceed in yields in the range 10–56% as in Ref. 17e. Fully functionalized amines gave better results as in Refs. 15a and 17f.
24. *Representative experimental procedure for enyne metathesis*: 0.65 g (2.90 mmol) of toluene-4-sulfonic acid but-3-ynyl ester (**7**) was dissolved in 5 mL of dry CH_2Cl_2. 1.72 g (5.80 mmol) of allyloxy-*tert*-butyl-diphenyl-silane (**8**) in 2 mL of CH_2Cl_2 were added. After addition of 0.238 g (0.290 mmol) of Grubbs' catalyst (**2**) in 8 mL of CH_2Cl_2, the mixture was stirred for 8 h at room temperature. Then, 0.19 g (0.435 mmol) of lead tetraacetate in 1 mL of CH_2Cl_2 was added and the reaction was stirred for 12 h at rt. The crude was concentrated under vacuum and purified chromatographically with hexane:EtOAc (10:1) on silica gel. 1.45 g (95%) of a mixture *E*:*Z* (1.1:1.0, **9**) were obtained on the basis of the ^{1}H NMR and ^{1}H–^{1}H COSY spectra.
9*Z*: ^{1}H NMR (200 MHz, $CDCl_3$): 7.78 (OTs, 2H, m); 7.68 (Ph(Si), 4H, m); 7.41 (Ph(Si), 6H, m); 7.37 (OTs, 2H, m); 5.76 (SiOCH$_2$C**H**CH, 1H, m), 5.72 (SiOCH$_2$CHC**H**, 1H, bd); 4.91 (=C**H**$_2$, 1H, s); 4.67 (=C**H**$_2$, 1H, s); 4.24 (SiOC**H**$_2$, 2H, bd, $J=6.3$ Hz); 4.05 (TsOC**H**$_2$, 2H, t, $J=6.8$ Hz); 2.43 (TsO, 3H, s); 2.41 (OTs, 3H, s); 2.34 (C**H**$_2$CH$_2$OTs, 2H, t, $J=6.8$ Hz); 1.08 (^{t}Bu(Me), 9H, s). ^{13}C NMR (25 MHz, $CDCl_3$): 144.7 (s), 139.1 (s), 135.5 (d), 133.8 (s), 133.5 (s), 130.8 (d), 130.6 (d), 129.7 (d), 129.6 (d), 127.8 (d), 127.7 (d), 117.4 (t), 68.6 (t), 61.0 (t), 36.1 (t), 26.8 (q), 19.2 (s). APcI (+) (m/z): 543 (M+Na)$^+$. **9*E***: ^{1}H NMR (200 MHz, $CDCl_3$): 7.78 (OTs, 2H, m); 7.68 (Ph(Si), 4H, m); 7.41 (Ph(Si), 6H, m); 7.37 (OTs, 2H, m); 6.23 (SiOCH$_2$CHC**H**, 1H, d, $J=16.1$ Hz); 5.62 (SiOCH$_2$C**H**, 1H, dt, $J=16.1$ Hz and 4.7 Hz); 5.13 (=C**H**$_2$, 1H, s), 5.03 (=C**H**$_2$, 1H, s); 4.24 (SiOC**H**$_2$, 2H, bd, $J=6.3$ Hz); 4.14 (C**H**$_2$OTs, 2H, t, $J=7.3$ Hz); 2.57 (C**H**$_2$CH$_2$OTs, 2H, t, $J=7.3$ Hz), 2.43 (OTs, 3H, s); 1.08 (^{t}Bu(Me), 9H, s). ^{13}C NMR (25 MHz, $CDCl_3$): 144.7 (s), 139.9 (s), 135.5 (d), 133.8 (s), 133.7 (s), 130.8 (d), 130.6 (d), 129.8 (d), 128.6 (d), 127.8 (d), 127.7 (d), 117.3 (t), 68.8 (t), 64.1 (t), 31.7 (t), 26.8 (q), 19.2 (s). APcI (+) (m/z): 543 (M+Na)$^+$.
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26. **10*Z***: ^{1}H NMR (200 MHz, $CDCl_3$): 7.68 (Ph(Si), 4H, m); 7.39 (Ph(Si), 6H, m); 5.85 (SiOCH$_2$C**H**, 1H, m); 5.81 (SiOCH$_2$CHC**H**, 1H, bd); 4.96 (=C**H**$_2$, 1H, s); 4.67 (=C**H**$_2$, 1H, s); 4.39 (SiOC**H**$_2$, 2H, d, $J=4.4$ Hz); 3.68 (COOC**H**$_3$, 3H, s); 3.19 (C**H**$_2$NHCOOCH$_3$, 2H, q, $J=6.5$ Hz); 2.21 (C**H**$_2$CH$_2$NH, 2H, t, $J=6.5$ Hz); 1.08 (^{t}Bu(Me), 9H, s). ^{13}C NMR: 157.1 (s), 142.3 (s), 135.5 (d), 133.7 (s), 130.9 (d), 130.8 (d), 128.7 (d), 127.7 (d), 116.6 (t), 64.3 (t), 51.9 (q), 39.4 (t), 32.5 (t), 26.8 (q), 19.1 (s). APcI (+) (m/z): 424 (M+H)$^+$. **10*E***: ^{1}H NMR (200 MHz, $CDCl_3$): 7.68 (Ph(Si), 4H, m); 7.39 (Ph(Si), 6H, m); 6.30 (-SiOCH$_2$CHC**H**-, 1H, d, $J=16.1$ Hz); 5.77 (SiOCH$_2$C**H**-, 1H, m); 5.06 (=C**H**$_2$, 1H, s); 4.97 (=C**H**$_2$, 1H, s); 4.29 (-SiOC**H**$_2$-, 2H, d, $J=6.3$ Hz); 3.65 (-COOCH$_3$-, 3H, s); 3.31 (C**H**$_2$NHCOOCH$_3$-, 2H, q, $J=6.5$ Hz); 2.41 (-C**H**$_2$CH$_2$NH-, 2H, t, $J=6.5$ Hz); 1.06 (^{t}Bu(Me), 9H, s). ^{13}C NMR: 157.0 (s), 141.6 (s), 135.5 (d), 133.7 (s), 132.8 (d), 130.9 (d), 130.8 (d), 116.6 (t), 61.0 (t), 51.9 (q), 39.4 (t), 37.0 (t), 26.8 (q), 19.1 (s). APcI (+) (m/z): 424 (M+H)$^+$.
27. **11*Z***: ^{1}H NMR (200 MHz, $CDCl_3$): 5.93 (1H, HOCH$_2$CHC**H**, d, $J=12.1$ Hz), 5.79 (1H, HOCH$_2$C**H**CH, dt, $J=12.1$ and 5.9 Hz), 5.10 (1H, =C**H**$_2$, s); 4.80 (1H, =C**H**$_2$, s), 4.70 (bs, N**H**); 4.28 (2H, HOC**H**$_2$CH, d, $J=5.9$ Hz); 3.66 (3H, COO**Me**, s); 3.32 (2H, C**H**$_2$NHCOOMe, m); 2.30 (2H, C**H**$_2$CH$_2$NHCOOMe, t, $J=6.3$ Hz); 2.20 (bs; O**H**). ^{13}C NMR: 157.2 (s), 141.7 (s), 132.3 (d), 130.7 (d), 117.0 (t), 59.1 (t), 52.1 (q), 39.4 (t), 37.6 (t). APcI (+) (m/z): 186 (M+H)$^+$. **11*E***: ^{1}H NMR (200 MHz, $CDCl_3$): 6.28 (1H, HOCH$_2$CHC**H**-, d, $J=16.1$ Hz); 5.95 (1H, HOCH$_2$C**H**CH-, dt, $J=16.1$ and 6.8 Hz), 5.12 (1H, =C**H**$_2$, s); 5.02 (1H, =C**H**$_2$, s), 4.70 (bs, N**H**); 4.23 (2H, HOC**H**$_2$CH, d, $J=6.8$ Hz), 3.66 (3H, COO**Me**, s); 3.32 (2H, C**H**$_2$NHCOOMe, q, $J=6.8$ Hz,); 2.44 (2H, C**H**$_2$CH$_2$NHCOOMe, t, $J=6.8$ Hz); 1.50 (bt; O**H**). ^{13}C NMR: 157.2 (s), 141.7 (s), 130.7 (d), 128.6 (d), 117.0 (t), 59.1 (t), 52.1 (q), 39.4 (t), 32.6 (t). APcI (+) (m/z): 186 (M+H)$^+$.
28. **4**: ^{1}H NMR (200 MHz, $CDCl_3$): 5.96 (BrCH$_2$CHC**H**, 1H, d, $J=10.7$ Hz); 5.92 (BrCH$_2$C**H**CH, 1H, dt, $J=10.7$ Hz and 7.8 Hz); 5.16 (=C**H**$_2$, 1H, s); 5.14 (=C**H**$_2$, 1H, s); 4.12 (BrC**H**$_2$CHCH, 2H, d, $J=7.8$ Hz); 3.67 (NHCOO**Me**, 3H, s); 3.27 (C**H**$_2$NHCOOMe, 2H, q, $J=6.3$ Hz); 2.35 (C**H**$_2$CH$_2$NH, 2H, t, $J=6.3$ Hz). ^{13}C NMR: 157.0 (s), 141.0 (s), 133.7 (d), 127.8 (d), 117.2 (t), 52.1 (q), 39.5 (t), 37.1 (t), 28.2 (t). FAB (+) (m/z): 249/251. **4*E***: ^{1}H NMR (200 MHz, $CDCl_3$): 6.30 (BrCH$_2$CHC**H**, 1H, d, $J=16.5$ Hz); 5.90 (BrCH$_2$C**H**CH, 1H, dt, $J=16.5$ Hz and 6.1 Hz); 5.18 (=C**H**$_2$, 1H, s); 5.05 (=C**H**$_2$, 1H, s); 4.10 (BrC**H**$_2$CHCH, 2H, bd, $J=6.1$ Hz); 3.67 (NHCOO**Me**, 3H, s); 3.30 (C**H**$_2$NHCOOMe, 2H, q, $J=6.3$ Hz); 2.42 (C**H**$_2$CH$_2$NH, 2H, t, $J=6.3$ Hz). ^{13}C NMR: 156.9 (s), 140.9 (s), 135.9 (d), 125.9 (d), 117.2 (t), 52.1 (q), 39.5 (t), 33.0 (t), 29.7 (t). FAB (+) (m/z): 249/251.