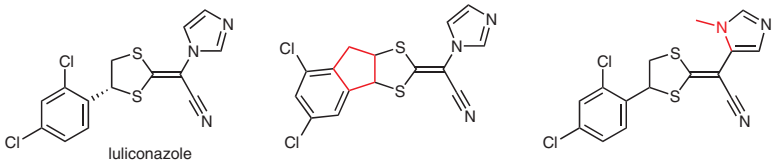
Synlett J. Gagnepain et al. Letter

Synthesis of Conformationally Locked and C-Linked Analogues of Imidazole-Based Ketene Dithioacetal Fungicides

Julien Gagnepain
Stephane Jeanmart
Damien Bonvalot
Olivier Jacob
Clemens Lamberth*

Syngenta Crop Protection AG, Chemical Research, Schaffhauserstrasse 101, 4332 Stein, Switzerland
clemens.lamberth@syngenta.com



Received: 25.09.2018
Accepted after revision: 05.11.2018
Published online: 03.12.2018
DOI: 10.1055/s-0037-1610341; Art ID: st-2018-b0614-l

Abstract First examples with the unknown tricyclic 4,8*b*-dihydro-3*aH*-indeno[1,2-*d*][1,3]dithiole ring system have been prepared. Also, imidazoles linked in ring position 5 to a ketene dithioacetal and 1,3-dithiane derivatives with an exocyclic cyano- and imidazole-substituted C–C double bond are completely new. All these compounds are either conformationally locked, C-linked or six-ring analogues of the antifungal agent luliconazole. Synthesis and fungicidal activity of these sterol biosynthesis inhibitors are reported.

Key words dithiolane, imidazole, C14-demethylase inhibitor, fungicide

14α-Demethylase belongs to the family of cytochrome P450 enzymes and facilitates one step within the biosynthesis pathway from the acyclic terpenoid squalene to the tetracyclic ergosterol, the major cellular membrane component of fungi. The inhibition of this enzyme leads to the formation of abnormal amounts of 14α-methylated sterol precursors and consequently to a depletion of ergosterol required for fungal tissue development. Inhibitors of 14α-demethylase (also called **D**e**M**ethylase **I**nhibitors, DMIs) found ample application in the prevention and treatment of fungal infections of human[1,2] and plants.[3,4] Interestingly, inhibition of 14α-demethylase is the only mode of action which is used for the control of fungal pathogens of both human and plants. A whole arsenal of DMIs, the conazoles, has entered the agrochemical and pharmaceutical market, in which a ring nitrogen of a heterocyclic pharmacophore is forming the essential binding to the iron atom of the heme cofactor in the active site of 14α-demethylase. Most of these active ingredients are either triazoles or imidazoles, the imidazole-based ketene dithioacetals constitute a very modern structural subtype within this mode of action class. Lanoconazole[5] (**1**) and luliconazole (**2**),[6] two examples with this special scaffold, are used as topical antimycotics against candidiasis,[7] onychomycosis,[8] *Malassezia*-associated skin diseases,[9] and dermatophytosis induced by *Trichophyton* spp.[10] Recently we have reported that some novel derivatives of luliconazole, such as the thienyl-analogue **3**, possess excellent activity against the plant pathogens *Alternaria solani* (causal agent of potato early blight), *Botryotinia fuckeliana* (causal agent of grey mold), *Erysiphe necator* (causal agent of grape powdery mildew) and *Zymoseptoria tritici* (causal agent of wheat leaf blotch).[11] In our attempts to further improve different properties of luliconazole (**2**), such as fungicidal efficacy, resistance profile, metabolic stability, we envisaged some structure modifications, which are completely novel amongst imidazole-based ketene dithioacetals. One idea was to freeze the rotational freedom of the phenyl ring by annulation to the dithiolane. This can be achieved by linking the phenyl not only via a direct bond, but also by an additional methylene bridge to the dithiolane ring. The resulting tricyclic ring system has been so far described only once,[12] but not with an exocyclic cyano- and imidazole-substituted C–C double bond. The concept of reducing the conformational flexibility of a biologically active compound by freezing a certain conformation through a ring-closure reaction, leading to so-called conformationally locked analogues with often increased binding affinity to the target, is well-known in the pharmaceutical and agrochemical lead optimization.[13–18]

Typically, in all commercialized antifungal and fungicidal DMIs with an imidazole pharmacophore, this five-membered ring is always unsubstituted. However, during our recent SAR study on imidazole-based ketene dithioacetals,[11] we found out that the 5-methylsubstituted lanoconazole derivative **4** was equipotent to the nonmethylated lead compound **1**. Therefore, another hypothesis dealt with the plan to link luliconazole's imidazole not via the typical ring nitrogen, as it is the case for lanoconazole and luliconazole,

but for the first time via the carbon atom in ring position 5, combined with the methylation of the sp^3 nitrogen, leading to **6** which is closely related to the highly active C-methylated imidazole derivative **4**. In this paper we report the synthesis of the conformationally restricted luliconazole analogue **5** and the C-linked imidazole derivative **6** which introduce for the first time completely new structural motifs into the DMI family (Figure 1).

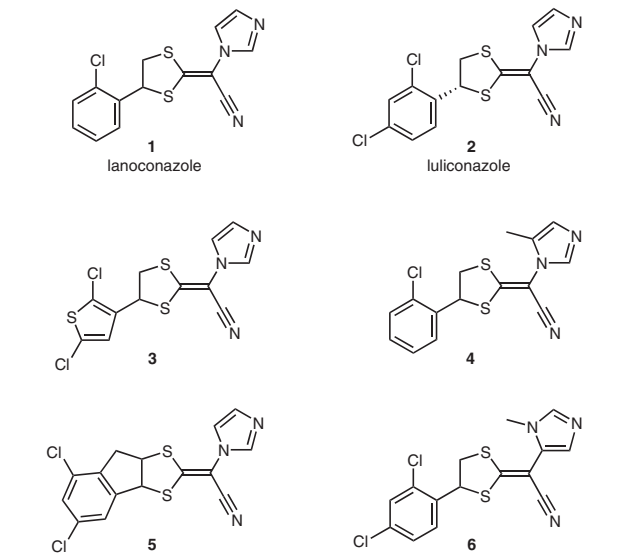
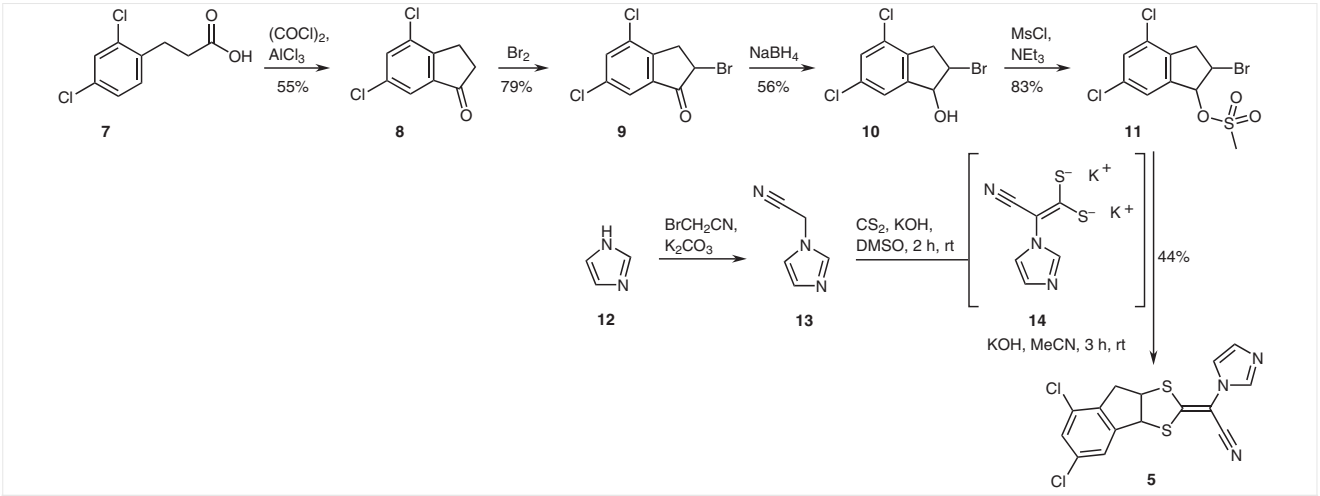


Figure 1 Lanoconazole (**1**) and luliconazole (**2**) as well as their fungicidally active analogues **3–6**

Our synthesis of the tricyclic luliconazole analogue **5** starts from 3-(2,4-dichlorophenyl)propionic acid (**7**),[19] which is cyclized to the dichloroindanone **8** by Friedel–Crafts acylation.[20,21] After the regioselective α-keto-bromination to **9**,[22] the reduction of the carbonyl function with sodium borohydride delivers the bicyclic bromohydrin **10**. This indanol derivative is then converted into the unstable α-bromomesylate **11**, which was then added to the freshly prepared dipotassium dithiolate **14** freshly prepared from 1*H*-imidazol-1-yl-ylacetonitrile (**13**),[23,24] carbon disulfide and potassium hydroxide. Although a dibromoindane derivative would be more stable than **11**, attempts to employ it in this special ring condensation were not successful. Both highly reactive intermediates, the α-bromomesylate **11** with two different nucleophilic leaving groups and the dipotassium dithiolate **14** furnish the desired tricyclic luliconazole analogue **5** as an inseparable mixture of *E* and *Z* isomers (Scheme 1).[25] The only other reference, which ever has reported one single compound with this 4,8*b*-dihydro-3*aH*-indeno[1,2-*d*][1,3]dithiole tricyclic ring system uses a completely different synthesis route.[12]

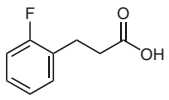
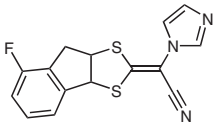
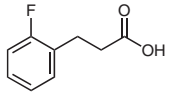
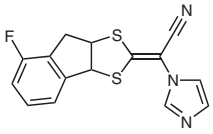
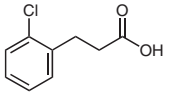
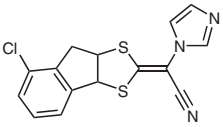
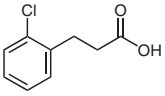
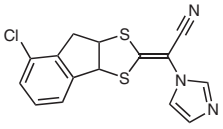
The reaction sequence shown in Scheme 1 could also be applied to other phenylpropionic acids, resulting in further examples with the 4,8*b*-dihydro-3*aH*-indeno[1,2-*d*][1,3]dithiole ring system. What was impossible for the dichloro derivative **5** succeeded for the tricyclic ketene dithioacetals resulting from 2-chloro and 2-fluorophenylpropionic acid, they could be separated into the *E* and *Z* isomers. As shown in Table 1, their physicochemical properties are completely different, the *E* isomers (Table 1, entries 1 and 3) are oils, whereas the *Z* isomers (Table 1, entries 2 and 4) are solids with relatively high melting points. Another general trend is that the *E* form was always the predominantly formed isomer.[25]

In our previously reported study on imidazole-based ketene dithiacetals we found that the lanoconazole analogue **4**, which has been methylated in imidazole ring position 5, is highly active whereas the corresponding 2- or 4-methylated derivatives were devoid of any efficacy.[11] Therefore we wanted to check the behavior of structurally related carbon-linked N-methylated imidazole-based ketene dithioacetals such as **6** against phytopathogens. We started the syn-

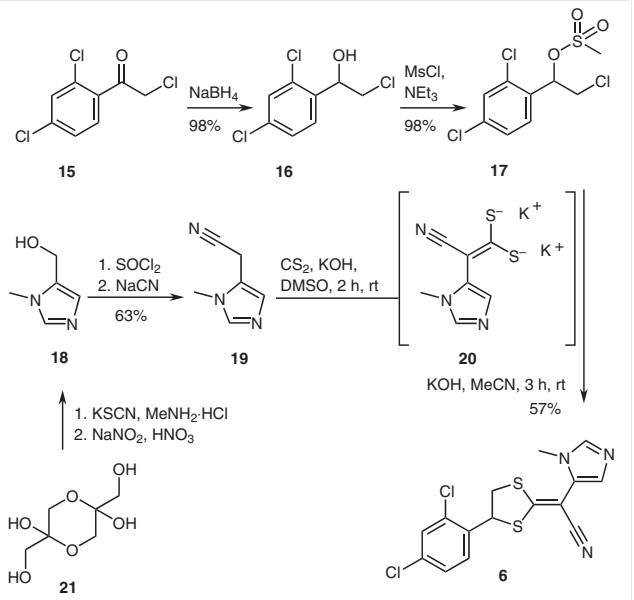


Scheme 1 Synthesis of the conformationally locked luliconazole analogue **5**

Table 1 Different Physicochemical Properties of *E* and *Z* Isomers of Tricyclic Imidazole-Based Ketene Dithioacetals

Entry	Arylpropionic acid	Dihydroindeno[1,3]dithiole derivative	Isomer	Analytical data
1			*E*	oil, LC-MS: Rt = 0.78 min; MS: *m/z* = 316 $[M + 1]^+$
2			*Z*	solid, mp 165–166 °C
3			*E*	oil, LC-MS: Rt = 0.94 min; MS: *m/z* = 332 $[M + 1]^+$
4			*Z*	solid, mp 216–218 °C

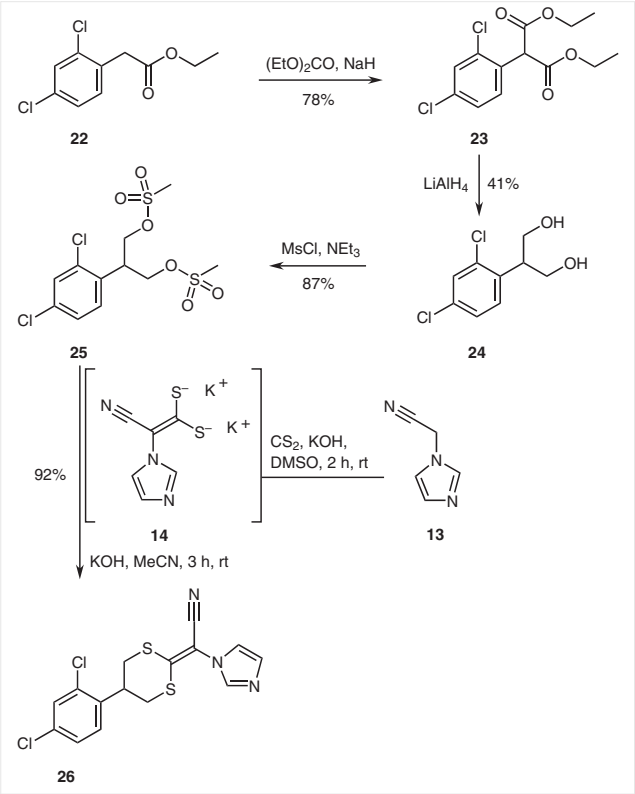
thesis of this luliconazole analogue with the sodium borohydride reduction of the phenacylchloride **15** to the chlorohydrine **16**.[26] Its mesylation leads to the reactive α-chloromesylate **17**,[27] which upon treatment with the dipotassium dithiolate **20** delivers the desired carbon-linked luliconazole derivative **6** as 1:1 *E*/*Z* mixture.[28] The preparation of the dithiolate **20** requires the rarely described 1-methyl-1*H*-imidazol-5-ylacetonitrile (**19**),[29] which can be obtained from dihydroxyacetone dimer **21** via the 5-hydroxymethylimidazol derivative **18** (Scheme 2).[30,31]



Scheme 2 Synthesis of the luliconazole analogue **6** with a C-linked imidazole

Finally, we also planned to replace the 1,3-dithiolane ring of luliconazole by a six-membered dithiane equivalent. The synthesis of the resulting six-ring analogue **26** of luliconazole is shown in Scheme 3. Ethyl 2,4-dichlorophenylacetate (**22**) is converted with diethyl carbonate under basic conditions into the diethyl 2,4-dichlorophenylmalonate (**23**).[32,33] Both ester functions of the phenylmalonate derivative **23** are then reduced with lithium aluminum hydride to the 1,3-diol **24**.[33,34] Methylsulfonylation of both alcohol functions furnishes the reactive intermediate **25** which after transformation with the dipotassium dithiolate **14** delivers the 1,3-dithiane **26**, the first luliconazole analogue with a six-ring dithioacetal (Scheme 3).

In conclusion we have achieved the synthesis of some completely novel 14α-demethylase inhibitor scaffolds, as tricyclic and six-ring cyano- and imidazole-substituted ketene dithioacetals have been unknown so far. We have checked for all new compounds their ability to control the economically important cereal pathogens *Blumeria graminis* (causal agent of wheat powdery mildew), *Zymospetoria tritici* (causal agent of wheat leaf blotch), and *Pyrenophora teres* (causal agent of barley net blotch). As it turned out the tricyclic ketene dithioacetal **5** as well as its four analogues from Table 1 showed strong efficacy especially against the wheat diseases powdery mildew and leaf blotch with the fluoro-substituted Z isomer (Table 1, entry 2) as most active example. In general, the E and Z isomers delivered similar potency. Also, the C-linked imidazole-based ketene dithioacetal **6** showed full control of the three phytopathogens at 60 ppm. Only the six-ring analogue **26** of luliconazole was nearly inactive.



Scheme 3 Synthesis of the luliconazole analogue **26** with a dithiane ring

Acknowledgment

The authors gratefully acknowledge the excellent synthetic contribution of Amelie Tessier.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610341.

References and Notes

(1) Peyton, L. R.; Gallagher, S.; Hashemzadeh, M. *Drugs Today* **2015**, *51*, 705.
(2) Heeres, J.; Meerpoel, L.; Lewi, P. *Molecules* **2010**, *15*, 4129.
(3) Worthington, P. In *Bioactive Heterocyclic Compound Classes: Agrochemicals*; Lamberth, C.; Dinges, J., Ed.; Wiley-VCH: Weinheim, **2012**, 129.
(4) Kuck, K.-H.; Stenzel, K.; Vors, J.-P. In *Modern Crop Protection Compounds*; Krämer, W.; Schirmer, U.; Jeschke, P.; Witschel, M., Ed.; Wiley-VCH: Weinheim, **2012**, 761.
(5) Niwano, Y.; Ohmi, T.; Seo, A.; Kodama, H.; Koga, H.; Sakai, A. *Curr. Med. Chem. Anti-Infect. Agents* **2003**, *2*, 147.
(6) Niwano, Y.; Ohmi, T.; Seo, A.; Kodama, H.; Kanai, K. *Recent Res. Dev. Antimicrob. Agents Chemother.* **2000**, *4*, 81.
(7) Niwano, Y.; Seo, A.; Kanai, K.; Hamaguchi, H.; Uchida, K.; Yamaguchi, H. *Antimicrob. Agents Chemother.* **1994**, *38*, 2204.
(8) Scher, R. K.; Nakamura, N.; Tavakkol, A. *Mycoses* **2014**, *57*, 389.
(9) Uchida, K.; Nishiyama, Y.; Tanaka, T.; Yamaguchi, H. *Int. J. Antimicrob. Agents* **2003**, *21*, 234.
(10) Koga, H.; Nanjoh, Y.; Kaneda, H.; Yamaguchi, H.; Tsuboi, R. *Antimicrob. Agents Chemther.* **2012**, *56*, 3138.
(11) Jeanmart, S.; Gagnepain, J.; Maity, P.; Lamberth, C.; Cederbaum, F.; Rajan, R.; Jacob, O.; Blum, M.; Bieri, S. *Bioorg. Med. Chem.* **2018**, *26*, 2009.
(12) Levesque, G.; Tabak, G.; Outurquin, F.; Gressier, J. C. *Bull. Soc. Chim. Fr.* **1976**, 1156.
(13) Murphy Kessabi, F.; Beaudegnies, R.; Quaranta, L.; Lamberth, C. *Tetrahedron Lett.* **2016**, *57*, 5511.
(14) Castilla, J.; Risquez, R.; Higaki, K.; Nanba, E.; Ohno, K.; Suzuki, Y.; Diaz, Y.; Ortiz Mellet, C.; Garcia Fernandez, J. M.; Castillon, S. *Eur. J. Med. Chem.* **2015**, *90*, 258.
(15) Shing, T. K. M.; Wong, A. W. H.; Li, H.; Liu, Z. F.; Chan, P. K. S. *Org. Biomol. Chem.* **2014**, *12*, 9439.
(16) Nayak, A.; Chandra, G.; Hwang, I.; Kim, K.; Hou, X.; Kim, H. O.; Sahu, P. K.; Roy, K. K.; Yoo, J.; Lee, Y.; Cui, M.; Choi, S.; Moss, S. M.; Phan, K.; Gao, Z.-G.; Ha, H.; Jacobson, K. A.; Jeong, L. S. *J. Med. Chem.* **2014**, *57*, 1344.
(17) Brant, M. G.; Wulff, J. E. *Org. Lett.* **2012**, *14*, 5876.
(18) Dixit, S. S.; Upadhayaya, R. S.; Chattopadhyaya, J. *Org. Biomol. Chem.* **2012**, *10*, 6121.
(19) Yale, H. L.; Spitzmiller, E. R. *J. Heterocycl. Chem.* **1978**, *15*, 1373.
(20) Sharma, A. K.; Subramani, A. V.; Gorman, C. B. *Tetrahedron* **2007**, *63*, 389.
(21) Rackelmann, N.; Matter, H.; Englert, H.; Follmann, M.; Maier, T.; Weston, J.; Arndt, P.; Heyse, W.; Mertsch, K.; Wirth, K.; Bialy, L. *J. Med. Chem.* **2016**, *59*, 8812.
(22) Zhang, R.; Dong, J.; Xu, Y.; Hua, W.; Wen, N.; You, Q. *Eur. J. Med. Chem.* **2009**, *44*, 3771.
(23) Litzinger, E. A.; Martasek, P.; Roman, L. J.; Silverman, R. B. *Bioorg. Med. Chem.* **2006**, *14*, 3185.
(24) De la Hoz, A.; Blasco, H.; Diaz-Ortiz, A.; Elguero, J.; Foces-Foces, C.; Moreno, A.; Sanchez-Migallon, A.; Valiente, G. *New. J. Chem.* **2002**, *26*, 926.
(25) Gagnepain, J.; Bonvalot, D.; Jeanmart, S. WO 2015011194, **2015**.
(26) Dulcevscaia, G. M.; Kravtsov, V. C.; Macaev, F. Z.; Duca, G. G.; Stingachi, E. P.; Pogrebnoi, S. I.; Boldescu, V. V.; Clapco, S. F.; Tiurina, J. P.; Deseatnic-Ciloci, A. A.; Lipkowski, J.; Liu, S.-X.; Decurtins, S.; Baca, S. G. *Polyhedron* **2013**, *52*, 106.
(27) de S. Fonseca, T.; Lima, L. D.; de Oliveira, M. C. F.; de Lemos, T. L. G.; Zampieri, D.; Molinari, F.; de Mattos, M. C. *Eur. J. Org. Chem.* **2018**, 2110.
(28) Bonvalot, D.; Jeanmart, S.; Gagnepain, J. WO2015003991, **2015**.
(29) Matulic-Adamic, J.; Watanabe, K. A. *Korean J. Med. Chem.* **1991**, *1*, 54.
(30) Przybyla, D.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2017**, 695.
(31) De Figueiredo, R. M.; Coudray, L.; Dubois, J. *Org. Biomol. Chem.* **2007**, *5*, 3299.
(32) Enoua, G. C.; Uray, G.; Stadlbauer, W. *J. Heterocycl. Chem.* **2012**, *49*, 1415.
(33) Chenevert, R.; Desjardins, M. *Can. J. Chem.* **1994**, *72*, 2312.
(34) Rios-Lombardia, N.; Busto, E.; Gotor-Fernandez, V.; Gotor, V. *Eur. J. Org. Chem.* **2010**, 484.