Tetrahedron: *Asymmetry* 28 (2017) 1423–1429

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Dual chiral silver catalyst in the synthetic approach to the core of hepatitis C virus inhibitor GSK 625433 using enantioselective 1,3-dipolar cycloaddition of azomethine ylides and electrophilic alkenes

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ARTICLE INFO

Article history:
Received 3 August 2017
Accepted 10 August 2017
Available online 30 August 2017

Dedicated to the memory of Dr. Howard Flack

ABSTRACT

The asymmetric 1,3-dipolar cycloaddition of an imino ester **5** with *tert*-butyl acrylate is catalyzed by a dual chiral silver(I) complex formed from a chiral phosphoramidite **14** and the chiral silver(I) binolphosphate (*R*)-**17**. This reaction is selected to achieve the synthesis of enantiomerically enriched key structures to access the third generation of GSK HCV inhibitors. The scope of this dual chiral catalytic system is analyzed by employing different imino esters and dipolarophiles, and also compared with the same cycloaddition reactions performed with the chiral phosphoramidite **14**·$AgClO_4$ complex.

1. Introduction

The enantioselective synthesis of pyrrolidines and proline derivatives constitutes a very important trend in organic chemistry due to their potential applications in many scientific fields.[1] From biological and medicinal viewpoints, molecules possessing antibiotic, antitumor, analgesic, and neuroexcitatory activities, have been widely described. However, the development of antiviral compounds (commercially available or in clinical studies) constitutes one of the main applications of these skeletons.[2,3] At the moment, many antiviral agents (used individually or in combination with another drugs) administrated to patients include a nitrogenated five-membered ring, for example, elbasvir, grazoprevir, velpatasvir, ombitasvir, paritaprevir, boceprevir, telaprevir and daclatasvir have recently been developed.[4] The complex skeleton of these molecules contrast with a family of prolinate derivatives **1**–**3** (Fig. 1) reported by GSK through successive evolutions.[5] These compounds act as polymerase inhibitors of the various strands of the virus responsible for Hepatitis C. Lower effective doses and reduced secondary effects converted these products to a promising treatment for hepatitis C virus (HCV) infected people.[6,7]

In our group, the asymmetric synthesis of the 1st generation **1**[8,9] and 2nd generation **2**[10] antiviral drugs employing diastereo-[8] and enantioselective[2,11] 1,3-dipolar cycloadditions (as the key-step) between the corresponding methyl iminoleucinate and a lactate derived acrylate,[8] or this imino ester with *tert*-butyl acrylate employing a chiral phosphoramidite-$AgClO_4$ catalytic complex[8] or a chiral dimeric Binap-gold(I) complex,[10] respectively, was developed. In both routes, the overall yields obtained were moderate to good and enantioselectivities were very high, especially in the case of the 2nd generation inhibitor (99% *ee*). Herein we report our efforts dedicated to building enantioselectively the core heterocyclic ring precursor of the GSK 625433 polymerase inhibitor **3**[12] and also a brief study of the scope and versatility of the newly developed catalyst.

2. Results and discussion

According to the classical retrosynthetic analysis of this family of compounds, we envisaged that the enantiomerically enriched cycloadducts of *endo*-**4** type were key compounds to access antiviral agent **3**. Initially, we designed two alternative approaches where the pyrazole ring was bonded in the starting imino ester (Scheme 1, eq. a) and a second retrosynthesis in which the pyrazole was introduced once the 1,3-dipolar cycloaddition had occurred (Scheme 1, eq. b). Starting imino ester **5a** could be generated under mild conditions from commercially available 3-(1-pyrazolyl)-L-alanine methyl ester hydrochloride, but significant amounts of the

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http://dx.doi.org/10.1016/j.tetasy.2017.08.011
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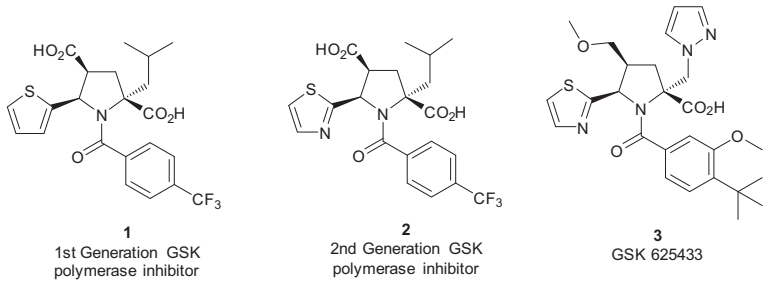
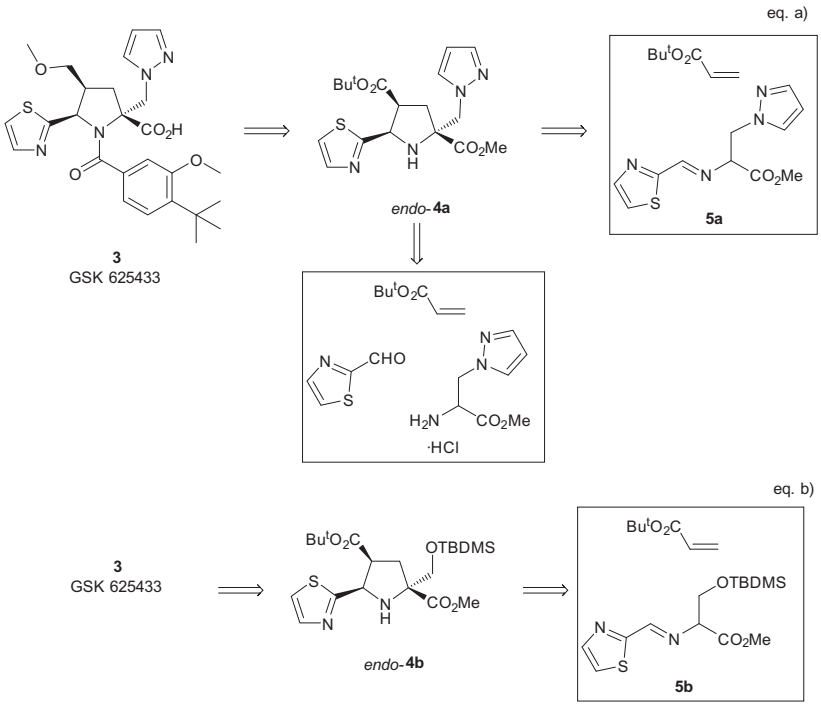


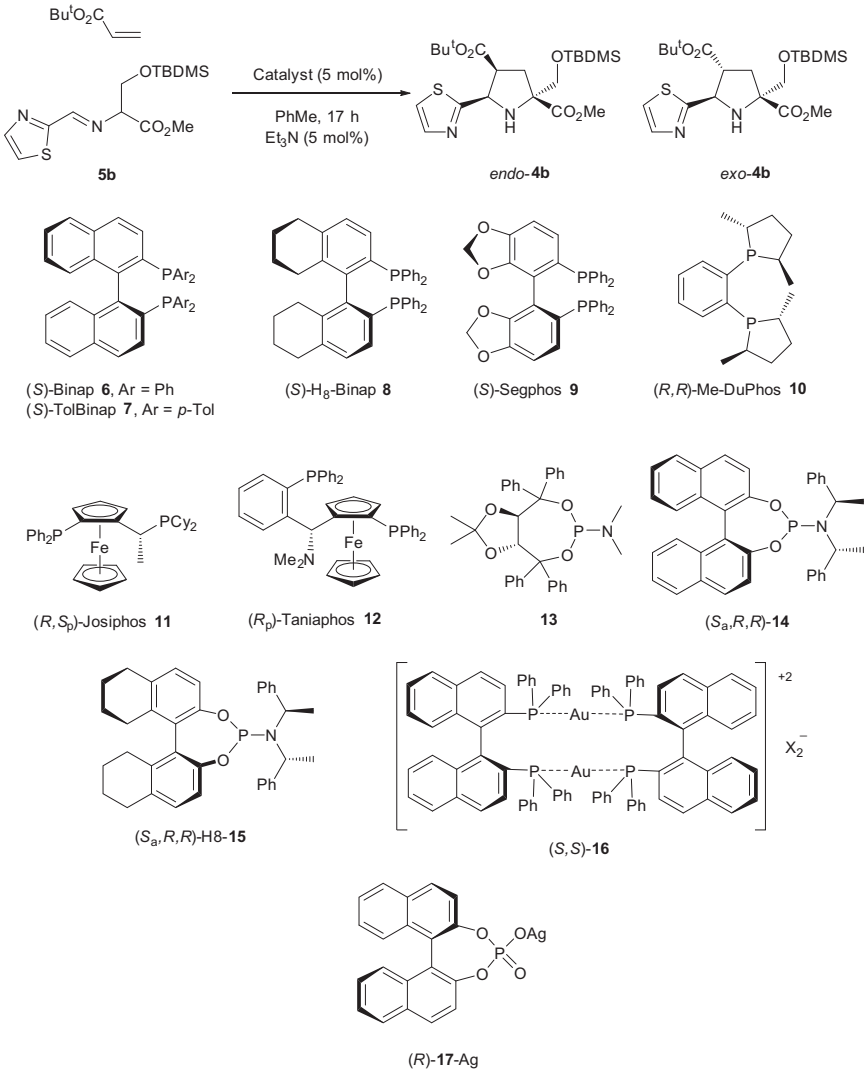
Figure 1. Family of GSK HCV inhibitors.



Scheme 1. Retrosynthetic analysis.

product, resulting from the β-elimination of pyrazole, were detected by ^{1}H NMR spectroscopy. The non-asymmetric multicomponent 1,3-dipolar cycloaddition was then tested employing *tert*-butyl acrylate, 2-thiazolecarbaldehyde and the amino ester, furnishing the undesirable β-elimination product.[13] This problem was overcome by employing the route starting from O-TBDMS serine derivative (Scheme 1, eq. b). Stable imino ester **5b** was much more appropriate to run the non-asymmetric cycloaddition and, in consequence, adequate to survey the enantioselective 1,3-dipolar cycloaddition. This imino ester **5b** was obtained in almost quantitative yield by reaction of 2-thiazolecarbaldehyde with the known compound O-TBDMS serine methyl ester[14] in DCM at room temperature for 19 h; it was then employed in the cycloadditions without any other purification (see Section 4).

Many chiral ligands and silver salts were tested at 5 mol% loading (Scheme 2 and Table 1) but always using toluene as the solvent (not registered in Table 1). The cycloadditions performed at room temperature involving Binap **6** afforded very good conversions but with moderate enantioselectivities (Table 1, entries 1–3).[15] The best silver salt was $AgSbF_6$, which gave at room temperature the desired compound *endo*-**4b** as an 85:15 mixture of diastereoisomers in 85:15 enantiomeric ratio (Table 1, entry 2). Lowering the temperature was not beneficial for this transformation (Table 1, entry 3).[16] Chiral ligands **7** and **8** did not improve the results achieved by Binap **6** and almost racemic compound *endo*-**4b** was isolated when AgOBz or $AgSbF_6$ were combined with chiral ligands **9**–**13** (these results are not included in Table 1). Phosphoramidite (S_a,*R*,*R*)-**14**·AgTFA complex and the analogous one formed with $AgSbF_6$ furnished identical conversions, diastereomeric and enantiomeric ratios (Table 1, entries 4 and 5). Analysis of the temperature was next studied (Table 1, entries 5–7) obtaining an increment of the diastereomeric ratio (up to 99:1, at −80 °C) but with a moderate enantioselection (80:20 at the same temperature). Analogous H8-chiral complex **15**·$AgSbF_6$ was not suitable for inducing very high enantiodiscrimination (Table 1, entry 8). Due to the dimeric gold species, (*S*,*S*)-**16**·TFA_2 being effective in the synthesis of the second generation GSK-agents,[10] it was used at 0 °C in the cycloaddition of *tert*-butyl acrylate and imino ester **5b**. The reaction was almost complete after 48 h reaction time to give *endo*-**4b** as the major diastereoisomer in 85:15 dr with modest enantioselectivity (78:26 er, Table 1, entry 9). The (*S*,*S*)-**16**·$(OBz)_2$ catalytic complex was not effective and afforded lower diastereomeric and enantiomeric ratios (Table 1, entry 10). However, the dual chiral catalyst **14**·Ag-(*R*)-**17**, formed by reaction of silver carbonate and chiral (*R*)-binol-phosphoric acid in toluene[17] for 1 h followed by the addition of phosphoramidite **14**, produced *endo*-



Scheme 2. Chiral ligands employed in the optimization study.

Table 1
Study of the reaction conditions for the synthesis of **4b**

Entry	Catalyst	T (°C)	Conv. (%)[a]	dr[a]	er[b]
1	**6**·AgTFA	25	>95	70:30	81:19
2	**6**·$AgSbF_6$	25	>95	85:15	85:15
3	**6**·$AgSbF_6$	0	>95	85:15	82:18
4	**14**·AgTFA	25	>95	90:10	66:34
5	**14**·$AgSbF_6$	25	>95	93:7	65:35
6	**14**·$AgSbF_6$	-20	>95	95:5	69:31
7	**14**·$AgSbF_6$	-80	>95	99:1	80:20
8	**15**·$AgSbF_6$	25	>95	99:1	59:31
9	**16**·$(TFA)_2$	0[c]	90	90:10	78:26
10	**16**·$(OBz)_2$	0[c]	95	85:15	76:24
11	**14**·Ag-(*R*)-**17**	25	>95	96:4	93:7
12	(R_a,*S*,*S*)-**14**·Ag-(*S*)-**17**	25	>95	95:5	8:92
13	(R_a,*S*,*S*)-**14**·Ag-(*R*)-**17**	25	>95	96:4	23:77
14	**14**·Ag-(*S*)-**17**	25	>95	90:10	75:25

[a] Determined by ^{1}H NMR of the crude reaction mixture. 10 h Reaction time.
[b] Determined by HPLC using chiral stationary phase columns.
[c] 48 h Reaction time.

cycloadduct **4b** at room temperature in excellent conversion and high diastereomeric and enantiomeric ratio (Table 1, entry 11). Lowering the temperature to −20 °C did not lead to any significant improvement of the enantiomeric ratio. The corresponding enantiomer *ent-endo*-**4b** was easily obtained by employing the enantiomeric chiral catalytic system (Table 1, entry 12). The configuration of these two enantiomeric forms of the dual chiral silver complex resulted in a matched combination for this transfor-

mation because the other two forms in the last two entries of Table 1 afforded lower enantiomeric ratios with excellent conversions. From the three last entries, it can be seen that the absolute configuration induced in the cycloadducts is strongly dependent of the axial chirality of the phosphoramidite ligand.

With compound *endo*-**4b** in hand (82% yield, 96:4 dr and 92:7 er), the next three steps were carried out in a sequential manner (Scheme 3). First, TBDMS was removed using three equiv. of tetrabutylammonium fluoride (TBAF, 1 M solution in THF) at room temperature for 3 h. Mesylation of the alcohol in the absence of trimethylamine avoided any undesirable ring expansion and after 2 h at 0 °C, sodium pyrazolide[18] was added at 0 °C. Cycloadduct *endo*-**18** was isolated after flash chromatography in 32% overall yield from *endo*-**4b**. The final access to molecule **3** can be achieved following known procedures described for this family of HCV inhibitors.[6,7,19]

The determination of the absolute configuration and the scope of the effectiveness of the double chiral activated complex **14**·Ag-(*R*)-**17** and **14**·$AgClO_4$ were studied simultaneously (Scheme 4 and Table 2). Initially, *N*-methylmaleimide was allowed to react with imino ester **19** (Ar = Ph, R^1 = H) under the optimized reaction conditions to yield product **20a** (Table 2, entry 1). The absolute configuration was assigned on the basis on the comparison of its retention time (HPLC using a chiral stationary phase column) with the retention time of the identical sample isolated from the reaction catalyzed by **14**·$AgClO_4$ complex.[8] This absolute configuration was confirmed by analyzing both the HPLC and specific optical data of all isolated compounds described in Table 2. The dual chiral catalyst **14**·Ag-(*R*)-**17** and **14**·$AgClO_4$ chiral complex also afforded similar results of **20b** and **20c** (Table 2, entries 2 and 3). However, the presence of a substituent at the α-position of the imino ester **19** caused steric difficulties to the bulky chiral entity of **14**·Ag-(*R*)-**17**. Thus, when alanine, leucine and phenylalanine derived imino esters **19** were employed with different dipolarophiles, the catalytic complex **14**·$AgClO_4$ afforded cycloadducts **20** with higher diastereomeric and enantiomeric ratios, although the chemical yields were similar to those obtained when using both catalytic complexes separately (Table 2, entries 4–6). It is noteworthy that compound **20d** is a potential novel HIV-1 integrase inhibitor,[20] while molecule **20e** is the key building block for the synthesis of the HCV inhibitor **1**.[6,8]

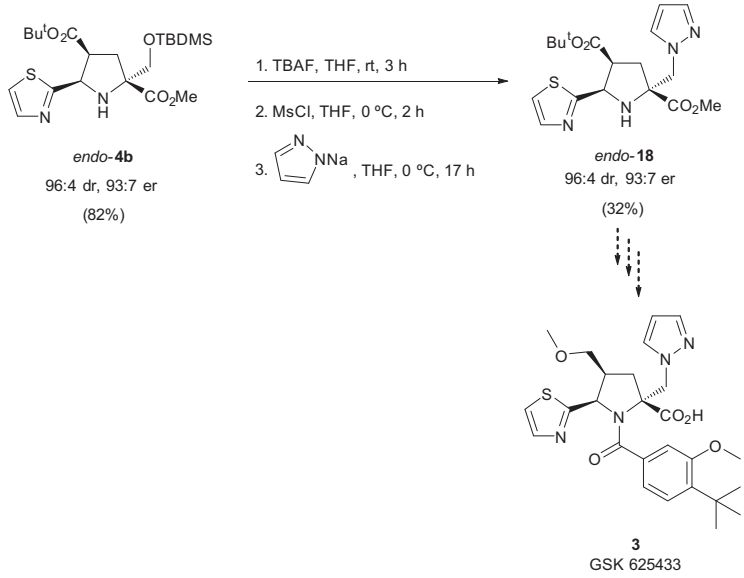
3. Conclusions

In conclusion, the modulation of the chiral catalyst **14**·Ag-(*R*)-**17** has been adapted to the effective approach of the imino ester and *tert*-butyl acrylate to access the enantiomerically enriched core of the antiviral agent GSK 625433 for the first time. A dual chiral catalyst was very important to achieve high enantioselection for this transformation unlike the results obtained by **14**·$AgClO_4$ complex. In the case of glycine imino esters both catalysts exhibited similar behaviors in the enantioselective 1,3-dipolar cycloaddition with dipolarophiles, although for sterically hindered imino esters (derived from α-substituted amino acids), the **14**·$AgClO_4$ complex should be used (Scheme 4).

4. Experimental

4.1. General

Melting points were determined with a Reichert Thermowar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra (recorded with an FT-IR

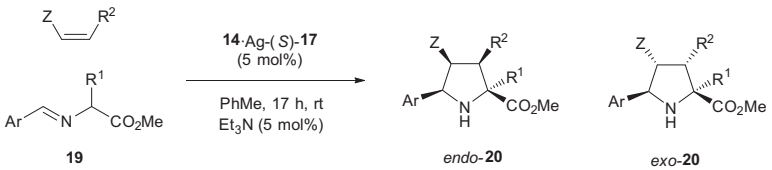


endo-**4b**
96:4 dr, 93:7 er
(82%)

endo-**18**
96:4 dr, 93:7 er
(32%)

3
GSK 625433

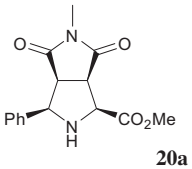
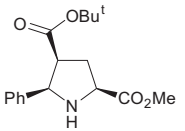
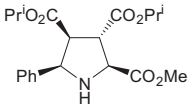
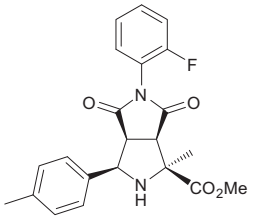
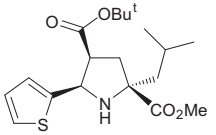
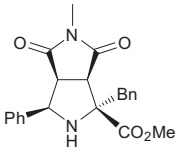
Scheme 3. Synthesis of the key enantiomer *endo*-**18** to access GSK 625433 polymerase inhibitor **3**.



19
endo-**20**
exo-**20**

Scheme 4. Scope of the reaction.

Table 2
Synthesis of cycloadducts **20** in the presence of **14**·Ag-(*R*)-**17** and comparison with the results obtained employing **14**·$AgClO_4$

Ent.	R^1	Ar	Dipolarophile	Structure	**14**·$AgClO_4$ (ref. 9)			**14**·Ag-(*R*)-**17**		
					Yield (%)[a]	dr[a]	er[b]	Yield (%)[a]	dr[a]	er[b]
1	H	Ph	*N*-methylmaleimide	 **20a**	80[c]	>98:2	>99:1	78[c]	>98:2	90:10
2	H	Ph	*tert*-Butyl acrylate	 **20b**	80[d]	>98:2	90:10	90[c]	>98:2	90:10
3	H	Ph	Diisopropyl fumarate	 **20c**	81[d]	>98:2	91:9	82[d]	90:10	89:11
4	Me	4-Me(C_6H_4)	*o*-FPM[e]	 **20d**	58[c]	95:5	61:39	58[c]	95:5	53:47
5	Bu^i	2-Thienyl	*tert*-Butyl acrylate	 **20e**	78[d]	>98:2	94:6	81[d]	95:5	76:24
6	Bn	Ph	*N*-Methylmaleimide	 **20f**	71[f]	>98:2	95:5	67[f]	95:5	73:27

[a] Determined by ^1H NMR of the crude reaction mixture. 10 h Reaction time.
[b] Determined by HPLC using chiral stationary phase columns for the *endo*-stereoisomer.
[c] Reaction performed at room temperature.
[d] Reaction performed at −20 °C.
[e] *o*-FPM = *N*-(*o*-fluorophenyl)maleimide. Compound **20d** was not prepared in Ref. 9.
[f] Reaction performed at 0 °C.

4100LE (JASCO) (PIKE MIRacle ATR) are listed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained with a Bruker AC-300 by using $CDCl_3$ as solvent and TMS as the internal standard, unless otherwise stated. Optical rotations were measured with a Perkin-Elmer 341 polarimeter. HPLC analyses were performed with a JASCO-2000 series equipped with a chiral stationary phase column (detailed for each compound in the main text) by using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase at 25 °C. Low-resolution electron impact (EI) mass spectra were obtained with a Shimadzu QP-5000 by injection or DIP, and high-resolution mass spectra were obtained with a Finnigan VG Platform or a Finnigan MAT 95S. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates and the spots were visualized under UV light (λ = 254 nm). Merck silica gel 60 (0.040–0.063 mm) was used for flash chromatography.

4.2. Synthesis of imino ester 5b

In a 10 mL flask were dissolved free O-TBDMS serine methyl ester[14] (357 mg, 1.5 mmol) and 2-thiazolecarbaldehyde (134 μL, 1.5 mmol) in anhydrous dichloromethane (10 mL) after which magnesium sulfate (200 mg) was added. The reaction was stirred at room temperature overnight and the organic phase was washed with brine, dried and evaporated to afford quantitatively the crude imine (492 mg, 1.5 mmol) as a pale yellow oil; IR (neat) ν_{max} 1743 cm^{-1}; ^{1}H NMR δ_H: 0.01, 0.05 (2 s, 6H, 2×MeSi), 0.85 (s, 9H, Me_3 C), 3.77 (s, 3H, MeO), 3.94 (dd, *J* = 10.5, 7.9 Hz, 1H, CH_2O), 4.16 (dd, *J* = 10.5, 5.3 Hz, 1H, C*H*CO_2Me), 4.26 (dd, *J* = 7.9, 5.3 Hz, 1H, CH_2O), 7.47, 7.93 (2 d, *J* = 3.1, 2H, HC=CH), 8.48 (s, 1H, HC=N); ^{13}C NMR δ_C: −5.4, −5.3 (Me_2Si), 18.2 (*C*Me_3), 25.8 (C*C*H_3), 52.3 (OMe), 63.5 (CH_2), 74.1 (CHCO), 122.1 (CHN), 144.8 (CHS), 158.4 (CNS), 166.3 (C=N), 170.1 (CO); MS (EI-GC) *m*/*z*: 328 (M^+, 1%), 271(80), 241 (11), 211 (13), 165 (42), 137 (100), 89 (51), 75 (77); HRMS calculated for $C_{20}H_{24}N_2O_3SSi$: 328.1277, found: 328.1266.

4.3. General procedure for the enantioselective 1,3-dipolar cycloaddition using dual catalyst 14·Ag-(*R*)-17. Synthesis of compounds *endo*-4b and 20

In a 10 ml vial covered by aluminum foil, Ag_2CO_3 (2.8 mg, 0.01 mmol), (*R*)-Binol-phosphoric acid (7 mg, 0.02 mmol) and toluene (3 mL) were added and the resulting mixture was stirred at room temperature for 1 h. Phosphoramidite (S_a,*R*,*R*)-**14** (10.8 mg, 0.02 mmol) was added and the reaction stirred for additional 40 min. The imino ester (0.4 mmol), the dipolarophile (0.4 mmol) and triethylamine (3 μL, 0.02 mmol) were then added sequentially and the reaction stirred at room temperature for 17 h. The solvent was evaporated and the crude product was purified by flash chromatography (*n*-hexane:EtOAc), affording cycloadducts *endo*-**4b** and **20**.

4.4. 4-(*tert*-Butyl) 2-methyl (2*R*,4*S*,5*R*)-2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate *endo*-4b

Sticky pale yellow oil, 119 mg (82%); $[\alpha]_D^{20}$ = −8.0 (*c* 0.8, CH_2Cl_2) for 93:7 er by HPLC (Chiralpak AD-H), *n*–hexane/*i*-PrOH: 90/10, (0.7 mL/min, λ 250 nm), t_{may}=8.3 min, t_{min}=9.2 min; IRν_{max}: 3345, 1727, 1677 cm^{-1}; ^{1}H RMN δ_H: 0.05, 0.09 (2 s, 6H, Me_2Si), 0.87 (s, 9H, Me_3 C), 1.19 (s, 9H, CO_2CMe_3), 2.16 (dd, *J* = 13.7, 8.1 Hz, 1H, CO_2MeCC*H*), 2.80 (dd, *J* = 13.7, 8.3 Hz, 1H, CO_2MeCC*H*), 3.00 (br. S, 1H, NH), 3.40 (ddd, *J* = 8.3, 8.1, 7.5 Hz, 1H, $CHCO_2t$Bu), 3.64 (d, *J* = 9.5 Hz, 1H, CH_2OTBDMS), 3.72 (s, 3H, CO_2Me), 3.79 (d, *J* = 9.5 Hz, 1H, CH_2OTBDMS), 4.93 (d, *J* = 7.5 Hz, NHC*H*), 7.24, 7.68 (2sd, *J* = 3.3 Hz, 2H, HC=CH); ^{13}C RMN δ_C: −5.6, −5.4 (Me_2Si), 18.2 (SiCMe_3), 25.8 (SiCMe_3), 27.7 (OCMe_3), 33.6 (CCH_2 C), 49.5 (*C*HCO_2tBu), 52.3 (CO_2Me), 61.5 (CHNH), 69.1 (CH_2OSi), 70.1 (*C*CO_2-Me), 80.9 (O*C*Me_3), 118.9 (CHS), 142.3 (*C*HNCSTh), 170.3 (NCS), 171.5, 174.6 (2×CO_2); MS (ESI) *m*/*z*: 456 (M^+, 2%); HRMS for C_{21}-$H_{36}N_2O_5Si$ required: 456.2112; found: 456.2108.

4.5. Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate 20a[9,21]

90 mg, 78%; $[\alpha]_D^{20}$ = +62.0 (*c* 1, CH_2Cl_2) for 90:10 er, $[\alpha]_D^{20}$ = +61.0 (*c* 1.18, CH_2Cl_2) for 90:10 er.[21]

4.6. 4-(tert-Butyl) 2-methyl (2*S*,4*S*,5*R*)-5-phenylpyrrolidine-2,4-dicarboxylate 20b[9,22]

84 mg, 90%; $[\alpha]_D^{20}$ = +22.5 (*c* 1.3, CH_2Cl_2) for 90:10 er, $[\alpha]_D^{20}$ = −26.8 (*c* 1.3, CH_2Cl_2) for 3:97 er (opposite enantiomer).[22]

4.7. 3,4-Diisopropyl 2-methyl (2*S*,3*S*,4*S*,5*R*)-5-phenylpyrrolidine-2,3,4-tricarboxylate 20c:[9]

66 mg, 82%; $[\alpha]_D^{20}$ = +30.9 (*c* 0.5, $CHCl_3$) for 89:11 er, $[\alpha]_D^{20}$ = +32.5 (*c* 0.5, $CHCl_3$) for 91:9 er.[9]

4.8. Methyl (1*S*,3*R*,3a*S*,6a*R*)-5-(2-fluorophenyl)-1-methyl-4,6-dioxo-3-(*p*-tolyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate 20d

Pale yellow oil, 92 mg, 58%. $[\alpha]_D^{20}$ = −3.5 (*c* 1.1, $CHCl_3$) for 61:39 er by HPLC (Chiralpak OD-H), *n*–hexane/*i*-PrOH: 50/50, (1 mL/min, λ 250 nm), t_{may}=9.7 min, t_{min}=14.7 min; IRν_{max}: 3370, 1771, 1690 cm^{-1}; ^{1}H RMN δ_H: 1.69 (s, 3H, MeCN), 2.32 (s, 3H, *Me*C_6H_4), 3.53 (d, *J* = 8.5 Hz, 1H, C*H*CMe), 3.40 (br. S, 1H, NH), 3.77 (dd, *J* = 10.0, 8.5 Hz, 1H, C*H*CHN), 3.87 (s, 3H, OMe), 4.92 (d, *J* = 10.0 Hz, 1H, CHN), 7.15–7.45 (m, 8H, Ar*H*); ^{13}C RMN δ_C: 22.3 (MeC_6H_4), 28.6 (*Me*CN), 49.7,51.8 (2×CHCO), 52.4 (CO_2Me), 59.2 (*C*NMe), 64.0 (NHC*H*), 126.6, 126.8, 127.3, 127.4, 128.1, 128.4, 128.6, 128.7, 129.0, 137.8 (Ar*C*), 169.1, 170.3, 172.0 (3×CO); MS (EI) *m*/*z*: 395 (M^+−1, 2%), 337 (45), 205 (100), 172 (18), 157 (10), 145 (70), 104 (10); HRMS for $C_{22}H_{21}FN_2O_4$ − H (M^+−1) required: 395.1407; found: 395.1403.

4.9. 4-(*tert*-Butyl) 2-methyl (2*S*,4*S*,5*R*)-2-isobutyl-5-(thiophen-2-yl)pyrrolidine-2,4-dicarboxylate 20e:[9] 95 mg, 81%

$[\alpha]_D^{20}$ = +23.2 (*c* 1, $CHCl_3$) for 76:24 er, $[\alpha]_D^{20}$ = +38.6 (*c* 1, $CHCl_3$) for 94:6 er.[9]

4.10. Methyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (20f):[9]

101 mg, 67%; $[\alpha]_D^{20}$ = −35.2 (*c* 0.8, $CHCl_3$) for 73:27 er, $[\alpha]_D^{20}$ = −74.2 (*c* 0.8, $CHCl_3$) for 95:5 er.[9]

4.11. Synthesis of 4-(*tert*-butyl) 2-methyl (2*R*,4*S*,5*R*)-2-[(1*H*-pyrazol-1-yl)methyl]-5-(thiazol-2-yl)pyrrolidine-2,4-dicarboxylate (*endo*-18)

Compound *endo*-**4b** (264 mg, 0.58 mmol) was dissolved in anhydrous in THF and tetrabutylammonium fluoride (1 M solution in THF) was added (1.75 mL, 1.75 mmol) at 0 °C. The reaction was then stirred at room temperature for three hours. The solvent was evaporated and ethyl acetate (10 mL) was added. The resulting solution was washed with brine, dried and evaporated to afford the intermediate alcohol, which was dissolved in anhydrous THF (5 mL). This new solution was cooled at 0 °C, after which triethylamine (89 μL, 0.64 mmol) was added and methanesulfonyl chlo-

ride was slowly introduced (54 μL, 0.64 mmol). Stirring was then continued for two hours at the same temperature, after which a 1:1 anhydrous DMF:THF solution (3 mL) containing sodium pyrazolide [1.75 mmol, obtained by mixing pyrazole (118 mg, 1.75 mmol) with sodium hydride (95%, 42 mg, 175 mmol)] was added and the reaction stirred at room temperature for 24 h. The solvent was evaporated and the residue purified by flash chromatography (*n*-hexane:EtOAc), affording cycloadduct *endo*-**18** as a pale yellow oil (70 mg, 32% overall yield). $[\alpha]_D^{20} = +7.7$ (*c* 0.6, $CHCl_3$) 93:7 er; IR ν_{max} 3065, 1728 cm^{-1}; ^1H NMR δ_H: 1.44 (s, 3H, CMe_3), 2.10 (dd, *J* = 10.8, 8.8 Hz, 1H, CCH_2 C), 2.58 (dd, *J* = 13.0, 8.8 Hz, 1H, CCH_2 C), 3.15 (m, 1H, CHCO), 3.65–372 (m with s at 3.73, 5H, NH, CH_2 N, OMe), 3.86 (d, *J* = 10.6 Hz, 1H, CH_2N), 4.86 (d, *J* = 8.5 H, 1H, H, CHN), 7.26 (m, 3H, CHCHNN, CHS), 7.64 (m, 2H, 2×C═CHN); ^{13}C NMR δ_C: 27.9 (CMe_3), 29.7 (CCH_2C), 52.1 (*C*HCO), 52.3 (OMe), 62.5 (CHNH), 67.3 (CH_2N), 70.2 (NCCO), 81.3 (CMe_3), 100.0 (*C*HCHNN), 119.1 (CHS), 128.1 (CHNN), 129.1 (CHNN), 142.5 (*C*HNCS), 171.5, 171.6, 174.5 (NCS, 2×CO); MS (EI-GC) *m*/*z*: 392 (M^+, 5%), 383 (10), 343 (15), 311 (24), 255 (100), 86 (13), 73 (13); HRMS calculated for $C_{18}H_{24}N_4O_4S$: 392.1518, found: 392.1509.

Acknowledgements

Financial support was provided by the Spanish Ministerio de Ciencia e Innovación (MICINN) (projects CTQ2010-20387, and Consolider Ingenio 2010, CSD2007-00006), the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC), the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P and CTQ2016-81797-REDC), the Generalitat Valenciana (PROMETEO 2009/039 and PROMETEOII/2014/017), and the University of Alicante.

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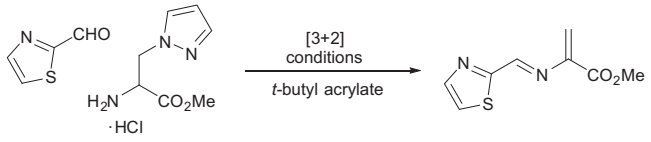

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