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Diels–Alder reactions with pyridine *o*-quinodimethanes generated from pyridine sulfolenes

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Abstract—An efficient route has been developed for the synthesis of polysubstituted 6,6-dioxo-6,7-dihydrothieno[3,4-*b*]pyridines **3**, which serve as excellent precursors for generation of the corresponding pyridine *o*-quinodimethanes. Following thermal extrusion of sulfur dioxide, these reactive species can be trapped in situ with electron rich, neutral, and electron deficient dienophiles. The regio and stereochemical structure of the resulting adducts was determined by NMR analysis.

1. Introduction

The chemistry of heteroaromatic *o*-quinodimethanes (Het-*o*-QDMs) **1** (Fig. 1) has gained increasing interest in the last decade.[1] A generally applied strategy is to generate these reactive species via thermolysis of heteroaromatic-fused 3-sulfolenes **2**.[2a–c] There are several advantages to the use of these sulfolene precursors. First, extrusion of SO_2 usually occurs already at moderately high temperatures and under neutral conditions so that the adducts formed via in situ trapping of the Het-*o*-QDMs with dienophiles can be isolated in good yield. A further merit resides in the acid character of the protons α to the sulfone group, which allows for introducing various substituents, e.g. dienophilic side chains. Until now three main routes leading to heteroaromatic-fused 3-sulfolenes have been reported: (1) reverse addition of SO_2 to Het-*o*-QDMs,[2a] (2) transformation of bis(halomethyl) heterocyclic compounds,[2b] and (3) annulation of a dihydrothiophene ring with a heterocyclic core.[2c] In a previous communication, we described an efficient route for preparing the functionalised pyridine sulfolene **3a**; initial thermolysis experiments carried out on **3a** involved

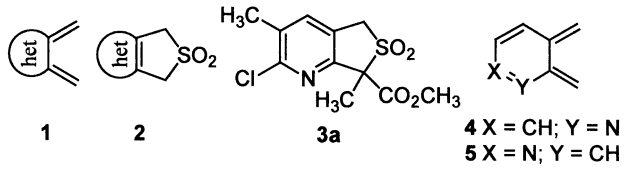


Figure 1.

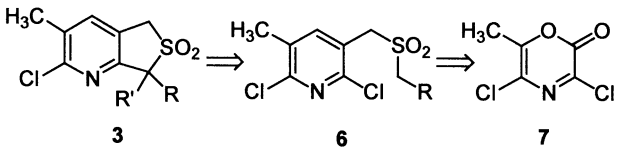
generation of the corresponding pyridine *o*-QDM of structural type **4** and in situ trapping of this reactive intermediate using various dienophiles.[3] We now wish to report further applications of this and similar pyridine *o*-QDM systems. So far, only a few reports have dealt with the application of pyridine *o*-QDMs of type **4** and its regioisomer **5**.[4]

2. Results and discussion

2.1. Synthesis of the pyridine *o*-QDM precursors

To generate pyridine sulfolenes of type **3**, we envisaged base-induced cyclisation of the corresponding sulfones **6** (Scheme 1). The polyfunctional pyridine ring system of **6** in turn can be constructed according to our general approach using cycloaddition of the oxazinone azadiene system **7** with alkynes, which proceeds with concomitant expulsion of carbon dioxide.[5]

Cycloaddition of oxazinone **7** with propargyl bromide was effected by heating in toluene to produce pyridine **8** as the only regioisomer in excellent yield (Scheme 2).[6] Subsequent treatment of **8** with sodium hydrogen sulfide resulted in a complex reaction mixture from which the desired thiol **9** could not be isolated. To solve this problem, first, bromide **8** was converted into a *S*-protected intermediate by reaction



Scheme 1.

Keywords: pyridines; sulfones; Diels–Alder reactions; quinonoid compounds.

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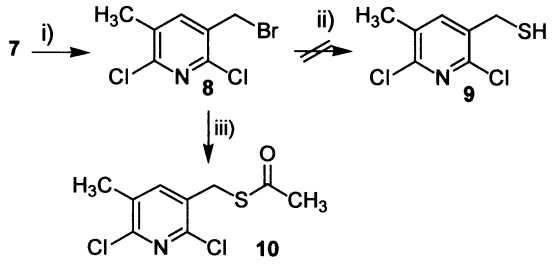


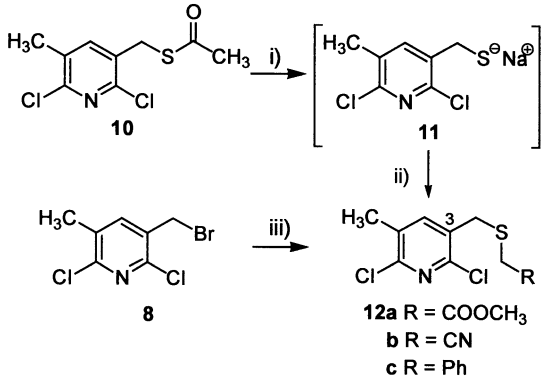
Scheme 2. Synthesis of thioester **10**. (i) 2 equiv. propargyl bromide, toluene reflux 8 h (98%), (ii) NaHS, MeOH reflux, (iii) 1.2 equiv. $HSCOCH_3$, 3 equiv. NEt_3, THF, room temperature, 20 min (98%).

with thiolacetic acid and an excess of NEt_3, affording thioester **10** in 98% yield.

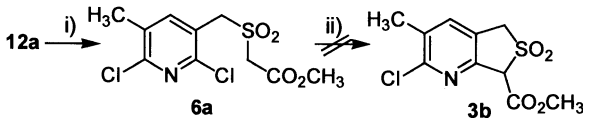
Deprotection of **10** was achieved by reaction with 1.2 equiv. of sodium methoxide in methanol to produce the desired thiol as the thiolate anion **11**. The latter could be alkylated in situ using the electrophilic reagents methyl chloroacetate, bromoacetonitrile and benzyl bromide to give the corresponding thioethers **12a**–**c** in 95, 95, and 75% yield, respectively (Scheme 3). Thioether **12a** also could be prepared directly from **8** in 88% yield by treatment with the commercially available methyl thioglycolate.

Oxidation of thioether **12a** to form the corresponding sulfone **6a** was accomplished in 85% yield by using *m*CPBA in CH_2Cl_2 (Scheme 4). However, several attempts to induce cyclisation of **6a**, using various basic conditions, failed to produce the corresponding pyridine sulfolene **3b**. This can probably be attributed to the weak nucleophilic character of the enolate anion formed, which is strongly stabilised by both the ester and sulfone group. Moreover, strong angular strain may be involved in folding back this planar anion above the pyridine ring for attack at the 2-Cl position.

Therefore, a different route was followed, which involved cyclisation of the more reactive anion obtained by treatment of thioether **12a** with KH in THF (Scheme 5). Due to the increased acidity of the α-proton remaining after cyclisation, an excess of KH was required to effect complete conversion of **12a** to a cyclic anion intermediate. This can



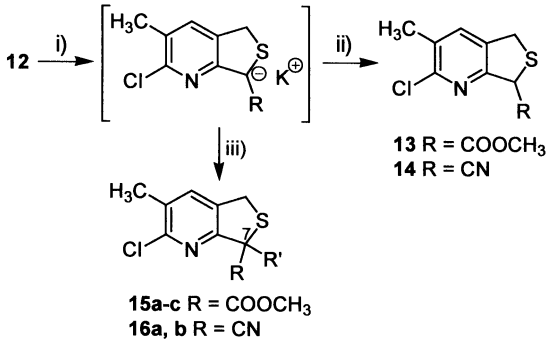
Scheme 3. Preparation of thioethers **12**. (i) 1.2 equiv. $NaOCH_3$, MeOH, room temperature, 15 min, (ii) 1.2 equiv. XCH_2R, MeOH, room temperature, 4 h, (iii) 1.1 equiv. $HSCH_2COOCH_3$, 3 equiv. NEt_3, THF, room temperature, 30 min.



Scheme 4. Attempted transformation of thioether **12a** to pyridine sulfolene **3b**. (i) 3 equiv. *m*CPBA, CH_2Cl_2, room temperature, 5 h (85%), (ii) base.

be converted to the free ester **13** by careful neutralisation, or captured in situ by reaction with suitable electrophiles to provide **15**. Thienopyridines **14** and **16** were prepared in a similar way from thioether **12b**. However, ring closure of thioether **12c** failed, probably due to the decreased acidity of the benzyl methylene group as compared to that of ester **12a** and nitrile **12b**.

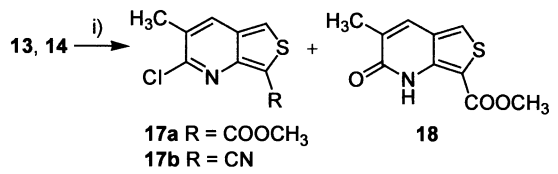
In several attempts to convert the cyclic thioethers into the desired pyridine *o*-QDM precursors, compounds **13** and **14** were treated with H_2O_2 in acetic acid or methanol, and with *m*CPBA in dichloromethane (Scheme 6). However, both reaction conditions were found to result in dehydrogenation of the dihydrothiophene ring to yield thienopyridines **17a**,**b** and a small amount of thienopyridinone **18**, the hydrolysis product of **17a**. Dehydrogenation probably proceeds via dehydration of the initially formed sulfoxide. Such dehydration of a sulfoxide intermediate cannot occur for 7,7-disubstituted compounds **15** and **16**. Hence, when submitted to oxidation with *m*CPBA in dichloromethane, the latter were converted in good yield to the desired pyridine



i) 2.2 eq. KH, THF, RT, 20 min. ii) NH_4Cl aq. sat., -78°C
iii) 1.2 eq. R'X, RT, 20 min.

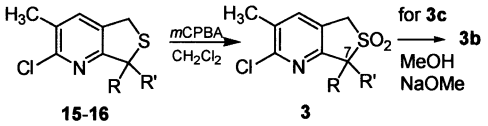
reagent	R'X	product	No (%)
12a	/	R= CO_2Me, R'= H	**13** (88)
	MeI	R= CO_2Me, R'= Me	**15a** (90)
	$ClCO_2Me$	R= R'= CO_2Me	**15b** (83)
	BnBr	R= CO_2Me, R'= Bn	**15c** (77)
12b	/	R= CN, R'= H	**14** (80)
	MeI	R= CN, R'= Me	**16a** (85)
	$ClCO_2Me$	R= CN, R'= CO_2Me	**16b** (65)

Scheme 5. Synthesis of cyclic thioethers **13**–**16**.



Scheme 6. Oxidation of cyclic thioethers **13** and **14**. (i) 3 equiv. *m*CPBA, CH_2Cl_2, room temperature, 3 h (**17a**: 80%, **17b**: 57%, **18**:15%).

Table 1. Oxidation of cyclic thioethers **15** and **16** to pyridine sulfolenes **3a–f**



No.	R	R′	Yield (%)
3a	$COOCH_3$	CH_3	93
3b	$COOCH_3$	H	85
3c	$COOCH_3$	$COOCH_3$	82
3d	$COOCH_3$	$CH_2C_6H_5$	80
3e	CN	CH_3	94
3f	CN	$COOCH_3$	62

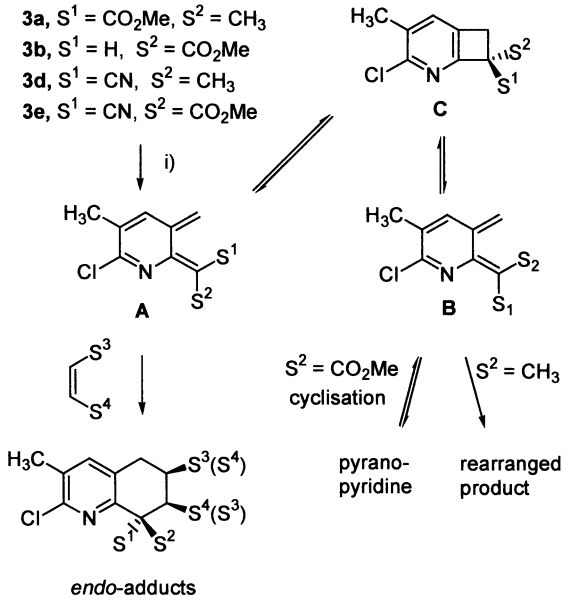
sulfolenes **3a**,**c–f** (Table 1). Finally, although oxidation of **13** failed to produce sulfolene **3b** (see above), this monosubstituted ester could be prepared in 85% yield starting from diester **15b**, which upon treatment with sodium methoxide in methanol smoothly lost one of the ester groups.

2.2. Generation of pyridine *o*-QDMs and their application to intermolecular Diels–Alder reactions

Thermal extrusion of sulfur dioxide from the 7-substituted pyridine sulfolenes **3** may produce terminally substituted dienes having either the *E*- or *Z*-configuration. According to a study of the electrocyclic (conrotatory) ring opening of substituted benzocyclobutenes,[7] an electron withdrawing group (e.g. aldehydes and ketones) tends to rotate inward, i.e. towards the other end of the diene, while an electron donating alkyl group would prefer an outward rotation. Ester and nitrile groups show an ambivalent character. When located at a monosubstituted diene end, these groups prefer an outward orientation. However, for *o*-QDMs bearing also an alkyl group at the disubstituted diene end, the ester and nitrile groups again are preferably oriented inward.

The thermolysis experiments were carried out by heating solutions of **3** in *o*-dichlorobenzene at 200°C in a sealed glass tube. To study the reactivity of the pyridine *o*-QDMs and their regioselectivity in cycloaddition reactions, thermolysis first was carried out in absence of a dienophile; subsequently, electron-poor, neutral, and electron-rich dienophiles were applied. In cases where the pyridine *o*-QDM system bears two different substituents at the same diene end, it was examined which geometric isomer **A** or **B** is preferably involved in: (a) the initial extrusion of sulfur dioxide, (b) intramolecular cyclisation and/or rearrangement of the pyridine *o*-QDM system, and (c) intermolecular cycloaddition reactions.

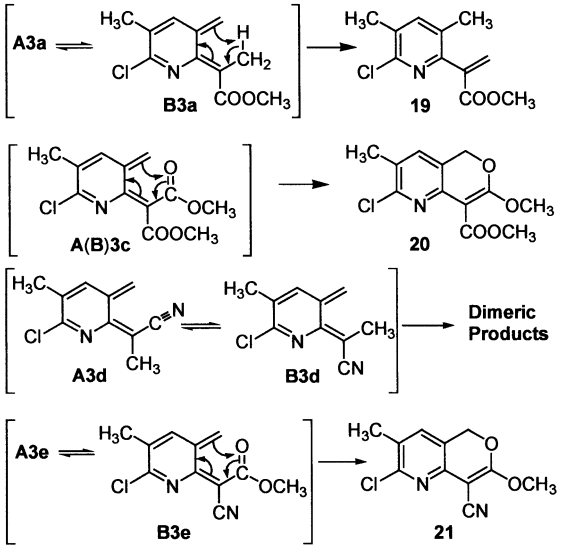
From the results given below, it appears that in the presence of a dienophile *endo*-addition proceeds from a preferred *o*-QDM intermediate **A** having an inward orientation of the S^1-substituent, in accordance with the preferences found for the electrocyclic opening of benzocyclobutenes.[7] However, when no dienophile is present, form **A** is converted slowly into its geometric isomer **B**, which then may undergo either electrocyclic ring closure or a rearrangement reaction. The conversion of **A** to **B** might



Scheme 7. Thermolysis of pyridine sulfolenes **3**. (i) *o*-Dichlorobenzene, 200°C, 15 h.

proceed via the bicyclic pyridine–cyclobutene intermediates **C** (Scheme 7). Indeed, the corresponding benzocyclobutenes also have been invoked as intermediates for interconversion between the *E*- and *Z*-isomers of the analogous benzene *o*-QDMs.[7]

2.2.1. Thermolysis in absence of a dienophile. In contrast to the intermolecular addition of dienophiles, which preferably occurs from *o*-QDM intermediates **A** (see below), form **B** was demonstrated as an intermediate in intramolecular cyclisation or rearrangement. Thus, thermolysis of pyridine sulfolene **3a** in the absence of a dienophile produced acrylate **19** in 78% yield (Scheme 8). This requires the generation of the *Z*-isomer **B3a**, followed by a 1,5-H shift.[8] The formation of pyranopyridine **20** (75% yield) from thermolysis of **3c** can be explained by an electrocyclic ring closure involving the carbonyl function



Scheme 8. Thermolysis of precursors **3a**,**c–e** in absence of a dienophile.

of an ester group in intermediate **A**(**B**)**3c**. Although a similar pyranopyridine also might form from *E*-isomer **A3a**, this could not be isolated. Indeed, pyranopyridine **20** was shown to revert to the *o*-QDM intermediate under thermolysis conditions (see below), in contrast to the irreversible 1,5-H shift observed for *Z*-isomer **B3a**. Thermolysis of sulfone **3d** gave a dimeric product (MH^+ 385) that was not further characterised. Following thermolysis of **3e**, pyranopyridine **21** was isolated in 80% yield. According to our general Scheme 7, this result can be explained by conversion of *Z*-isomer **A3e** with inward orientation of the linear nitrile group to the less stable *E*-isomer **B3e**. Although the latter exhibits a large steric repulsion between the ester and methylene groups, it may be stabilised by subsequent electrocyclic ring closure. Evidently, such ring closure is not feasible for *Z*-isomer **A3e** as this would require the insertion of a cumulene with diagonal C-atom in a six-membered ring.

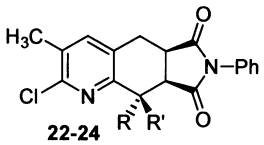
2.2.2. Intermolecular Diels–Alder reaction with *N*-phenylmaleimide (NPMA). Thermolysis of sulfolene **3a** in the presence of NPMA afforded adduct **22** as a single stereoisomer (88%). The stereostructure of **22** was established by X-ray diffraction as reported in our previous communication.[3] In a similar way, NPMA adducts **23** (85%) and **24** (65%) were produced from the thermolysis of precursors **3c** and **3d**, respectively (Table 2).

Since NPMA is known to add preferentially in the *endo*-mode, cycloaddition must proceed via *E*-isomers **A3a** and **A3d** to give exclusively the *endo*-adducts **22** and **24**. Hence, when related to the intramolecular reaction of *Z*-isomer **B3a** involving a 1,5-H shift, these results indicate that the geometric isomers **A** are the primarily formed pyridine *o*-QDM intermediates. Subsequent conversion of **A** into **B** might proceed via pyridocyclobutene **C** (see general Scheme 7) but presumably, this process is relatively slow as compared to the addition of NMPA.

The thermolysis of diester **3c** and the in situ Diels–Alder reaction with NPMA were conducted in *o*-dichlorobenzene at 160°C in two different ways: NPMA was added either before extrusion of sulfur dioxide or after conversion of **3c** to pyranopyridine **20**. In both cases, the same adduct **23** was isolated. This experiment demonstrates that interconversion of pyranopyridine **20** and the *o*-QDM intermediate **A**(**B**)**3c** is possible at 160°C.

Fig. 2 shows the structures of two pairs of boat conformers corresponding to the diastereomeric adducts **24**,**24′** derived

Table 2. Adducts formed in Diels–Alder reactions of **3a**,**c**–**d** with NPMA



22-24

Adduct	R	R′	Yield (%)
22	$COOCH_3$	CH_3	88
23	$COOCH_3$	$COOCH_3$	85
24	CN	CH_3	65

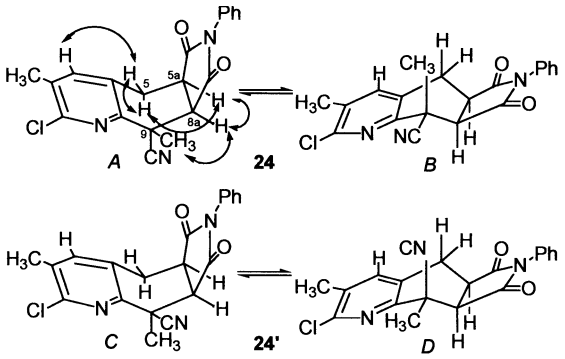
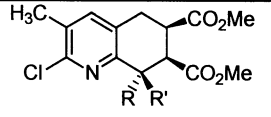
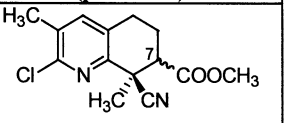
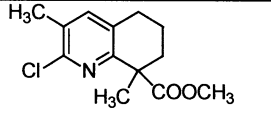
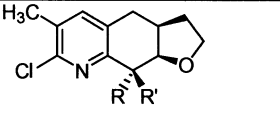
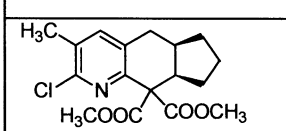
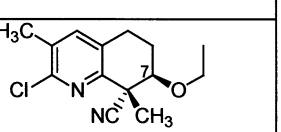


Figure 2. Two pairs of boat conformers for the all-*cis*-adduct **24** and the *trans*, *cis*-adduct **24′**.

from *endo*-addition of NMPA to either the *Z*-isomer **A3d** or the *E*-isomer **B3d**. By analogy to the NPMA adduct **22**, a *cis*-orientation was expected for the 9-methyl and carbonyl groups as in **24**, which corresponds to *endo*-addition of *Z*-isomer **A3d**. This was confirmed by NOESY analysis, which revealed that adduct **24** occurs as the boat conformer *A*. A strong NOE was found for the protons of the *trans*-oriented 9-methyl group and H-8a, in accordance with conformer *A* but not with *B*. Conformer *B* could be dismissed further on the basis that no NOE was observed between H-5ax and the axial 9-methyl protons. Conformer *D* of **24′** would require a NOE interaction of H-5eq with both H-4 and the *cis*-disposed proton H-5a, of which the latter was missing. Finally, boat form *C* was excluded since no NOE was found between H-5ax and the protons of the axial 9-Me group. Moreover, *E*-isomer **B3d** is expected to undergo a 1,5-H shift as observed for **B3a**.

2.2.3. Further Diels–Alder reactions. Further Diels–Alder reactions of pyridine *o*-QDMs generated from pyridine sulfolenes **3a**–**d** were conducted with various dienophiles to yield adducts **25**–**33** (Table 3).

Table 3. Adducts formed in Diels–Alder reactions of **3a**–**d** with other dienophiles

adduct (precursor)	adduct (precursor)
 **25 (3a)** R=CO_2Me; R'=Me (61%) **26 (3b)** R= H; R'= CO_2Me (73%)	 **29 (3d)** (70%)
 **27**[a] **(3a)**	 **30 (3a)** R=CO_2Me; R'=Me (55%) **31 (3c)** R= R'= CO_2Me (75%) **32 (3d)** R= CN; R'= Me (67%)
 **28 (3c)** (60%)	 **33 (3d)** (63%)

[a] This product could not be purified.

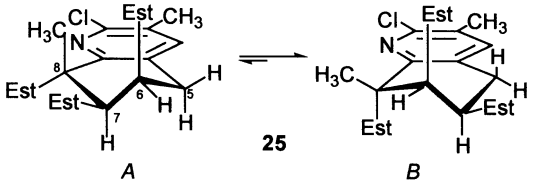


Figure 3. Half-chair conformers for *trans*, *cis*-adduct **25**.

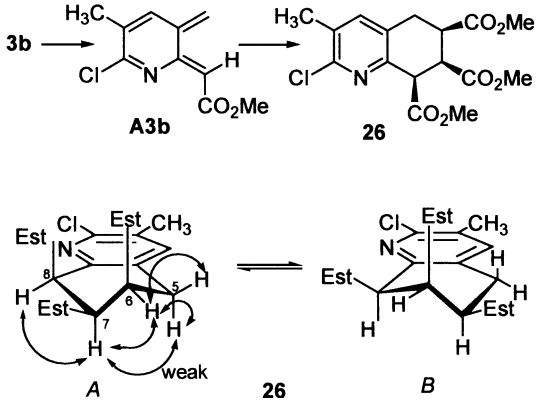
From analogy to the reaction of **3a** with NPMA, *E*-isomer **A3a** can be postulated as an intermediate in the cycloaddition with dimethyl maleate. Since this dienophile also adds preferably in the *endo*-mode, the *trans*,*cis*-adduct **25** is to be expected. Adduct **25** may exist as two half-chair forms *A* and *B* having an axial and equatorial orientation of the ester group on C-8 (Fig. 3). The prevalence of conformer *B* is demonstrated by the coupling values $^3J_{6-5eq}$=6.5 Hz and $^3J_{6-5ax}$=11.5 Hz. The high ^3J value for H-5ax and H-6 reveals a *trans*-diaxial orientation. Hyperchem calculations[9] suggest that conformer *B* is energetically favoured over *A*, which shows a severe 1,3-diaxial repulsion between the 8-methyl substituent and the ester group in 6-position (energy difference ca. 2 kcal/mol).

From ^{1}H NMR and NOESY analysis of adduct **26**, an all-*cis* disposition was inferred for the three ester groups, consistent with *endo*-addition of *Z*-diene **A3b** (Scheme 9). The NOE observed for H-7 and H-8 is consistent with the expected *cis*-relationship. A favoured conformational structure *A* was indicated by a further NOE relating both protons H-5 with H-6 and a weak NOE between the axial proton H-7 and H-5ax. The latter correlation was confirmed by the NOE-diff spectrum, which upon homonuclear decoupling of H-7 displayed a clear NOE with H-5ax. Overall, the NOE measurements suggest the existence of adduct **26** as a major conformer *A*. Yet, an equilibrium with a minor form *B* seems likely in view of the coupling values $^3J_{6-5ax}$=8.4 Hz and $^3J_{6-5eq}$=6.3 Hz.

Reaction of **3a** with ethene at elevated pressure afforded a small amount of adduct **27**, which however could not be adequately purified. From the reaction of **3a** with cyclopentene only the rearranged product **19** was isolated in 78% yield. Apparently, Diels–Alder reactions proceed rather slowly when using neutral dienophiles. This results in conversion of the *E*-isomer **A3a** into the *Z*-isomer **B3a**, which is subject to a competing 1,5-H shift to form **19**. However, addition of cyclopentene proved to be successful when such a competing pathway cannot occur as for the diester *o*-QDM intermediate **A**(**B**)**3c** derived from diester **3c**. Although the latter was shown to undergo electrocyclic ring closure to form pyranopyridine **20**, this process can be reversed and adduct **28** was isolated in 60% yield.

To study the regioselectivity of the Diels–Alder reaction some unsymmetrical dienophiles, i.e. methyl acrylate, 2,3-dihydrofuran and ethyl vinyl ether, were applied. Addition of methyl acrylate to the pyridine *o*-QDM system derived from **3d** furnished adduct **29** as a single regio and stereoisomer. Regiochemical assignment of this adduct was based on the multiplicity (dd) observed for H-7 in the ^{1}H NMR spectrum, showing that the ester function was in position 6. Cycloaddition to the initially formed *E*-diene **A3d** could produce either the *exo*- or *endo*-adduct **29′** or **29″**, corresponding to half-chair conformers *A*,*B* and *C*,*D* (Fig. 4). The ^3J values found for coupling between H-7 and H-6ax (10 Hz) and between H-7 and H-6eq (3 Hz) indicate that the product exists as a preferred half-chair conformer *A* or *C*. The occurrence of *A* corresponding to the *exo*-adduct **29′** was suggested by NOEs relating H-7 with both H-6eq and the 8-methyl group. However, these NOEs might also be attributed to some contribution of form *D* corresponding to an *endo*-adduct. Hence, at this point, definite assignment of stereochemical structure **29′** appears unjustified, especially in view of the exceptional *exo*-addition mode implied for methyl acrylate.

Reaction of the electron-rich dihydrofuran with monoester **3a**, diester **3c**, and nitrile **3d** in each case produced a single compound (**30**–**32**, respectively) with the O-atom in position 7 of the quinoline moiety. On thermolysis of **3a** rearranged product **19** was also formed. The regiochemical structure of the adducts **30**–**32** again was assigned from the ^{1}H NMR spectra, which displayed a doublet signal for H-9a corresponding to a single coupling with the other angular proton H-3a. In our previously reported NOESY analysis of dihydrofuran adduct **30**,[3] the latter was shown to exist as the (3a,9a)-ax,ax boat conformer *A*. This corresponds to *endo*-addition of dihydrofuran to the *E*-isomer **A3a** as observed with NPMA (Fig. 5).



Scheme 9. Thermolysis of **3b** and Diels–Alder reaction with dimethyl maleate to form *endo*-adduct **26**.

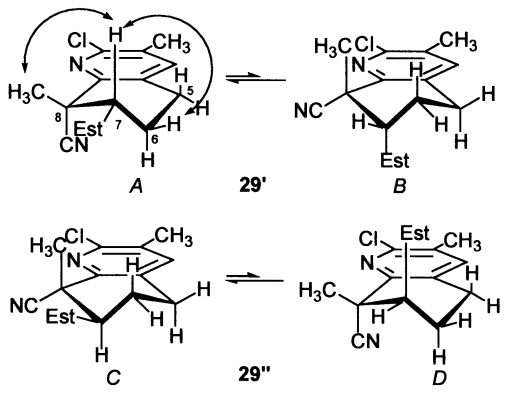


Figure 4. Two pairs of half-chair conformers corresponding to the *exo*-adduct **29′** and the *endo*-adduct **29″**.

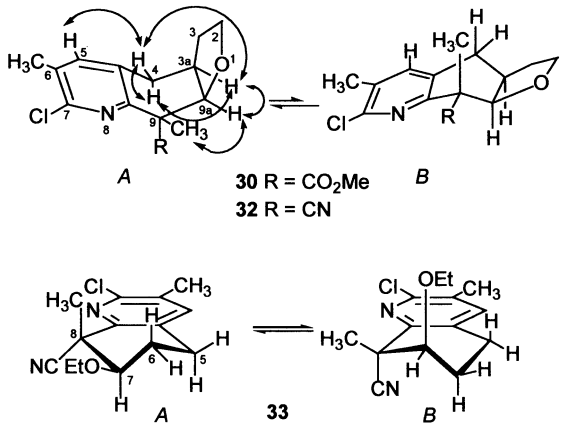


Figure 5. Pairs of boat and half-chair conformers corresponding to *endo*-adducts **30**, **32**–**33**.

The relative stereochemistry of dihydrofuran adduct **32** was assigned in a similar way on basis of NOE measurements and ^{3}J coupling constants in the ^{1}H NMR spectrum. Although the expected *endo*-adduct can exist as two boat conformers *A* and *B*, one preferred form was indicated by the differentiation found between H-4ax and H-4eq. In the NOESY spectrum (Fig. 5), only the latter proton gives a NOE with the aromatic proton H-5. Both H-4 protons show a strong NOE with H-3a, while H-9a correlates with the *trans*-disposed 9-methyl group. These results can be accommodated only if both angular protons H-3a and H-9a have an equatorial position as in structure *A*. The *cis* and *trans* coupling constants, $^{3}J_{3a-4ax}$=7.2 Hz and $^{3}J_{3a-4eq}$=1.8 Hz, correspond to a dihedral angle of approximately 40 and 80°, respectively, as estimated from model calculations for conformational structure *A*.[9]

Reaction of ethyl vinyl ether with precursor **3d** equally produced only one adduct **33**, having again the ethoxy substituent in position 7. Although an *endo*-adduct structure was assumed by analogy to the dihydrofuran adduct, this could not be substantiated by NMR spectral data. Proton H-4 gives a NOE with both protons H-5, indicating that compound **33** does not exist as a single half-chair, but rather as a conformational mixture of two half-chair forms. From the coupling constants $^{3}J_{7-6eq}$=2.4 Hz and $^{3}J_{7-6ax}$=8.0 Hz (but $^{3}J_{5-6ax}$=$^{3}J_{5-6eq}$=6.6 Hz), one can infer that conformer *A* having an axial H-7 is slightly favoured.

Using semi-empirical calculations based on the Frontier Molecular Orbital (FMO) method, we tried to rationalise the product distribution of the cycloadducts obtained from unsymmetrical dienophiles. For the electron-poor dienophile methyl acrylate the $HOMO_{diene}$–$LUMO_{dienophile}$ interaction is only slightly favoured (0.8 eV) relative to the 'inverse electron demand' interaction $LUMO_{diene}$–$HOMO_{dienophile}$ so that both pathways may compete. However, from the relative size of the orbital coefficients the same regioselectivity was predicted, corresponding to the experimentally observed 7-substituted quinoline derivative. For the electron-rich dihydrofuran the inverse electron demand interaction $LUMO_{diene}$–$HOMO_{dienophile}$ largely (ca. 2.4 eV) predominates, again favouring an adduct with the O-atom in position 7 of the quinoline moiety.

3. Conclusion

In this work, pyridine sulfolenes **3a**–**f** are shown to be easily accessible from the oxazinone **7**. Thermolytic extrusion of sulfur dioxide from these precursors produces the corresponding pyridine *o*-QDM intermediates, which can be trapped in situ with electron-poor (NPMA, dimethyl maleate, methyl acrylate), neutral (ethene, cyclopentene), and electron-rich (dihydrofuran, ethyl vinyl ether) dienophiles. These intermolecular Diels–Alder reactions generally proceed via an *endo*-transition state, with the reaction of **3d** and methyl acrylate as a possible exception. The primary pyridine *o*-QDM intermediate formed from 7,7-disubstituted (ester or nitrile and alkyl) sulfone precursors apparently has an inward orientation for the ester or nitrile function and an outward orientation for the larger alkyl group. Upon thermolysis of the monosubstituted ester precursor **3b**, the larger (ester versus H) group again prefers an outward orientation. However, the primary *o*-QDM intermediate (*E*-isomer) generated from the disubstituted (Me, CO_2Me) precursor **3a** apparently transforms slowly into the *Z*-isomer. For slowly reacting dienophiles like cyclopentene this results in a competing 1,5-H shift to form rearranged product **19** as an important side reaction.

4. Experimental

4.1. General methods

Infrared spectra were recorded on a Perkin–Elmer 297 grating IR spectrophotometer and a Perkin–Elmer 1720 Fourier transform spectrometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker WM 300 or on a Bruker AMX 400 instrument. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run using a Hewlett Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. For TLC and column chromatography analytical plates (Alugram Sil G/UV_{254}) and 70–230 mesh silica gel 60 (E.M. Merck) were used, respectively. Melting points were determined using a Reichert-Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Microanalyses were performed by Janssen Pharmaceutica.

4.1.1. Synthesis of [(2,6-dichloro-5-methyl-3-pyridyl)-methyl]thioacetate (10). To a stirred solution of 10 g of pyridine **8** and 3.8 mL (1.2 equiv.) thiolacetic acid in 200 mL of CH_2Cl_2 under an inert atmosphere was added dropwise 16.4 mL (3 equiv.) of NEt_3. After reaction at room temperature for 20 min, 50 mL of water was added. The reaction mixture was then extracted with CH_2Cl_2 (3×50 mL), the organic layer dried with $MgSO_4$, and the solvent evaporated. The residue was purified by column chromatography (CH_2Cl_2) affording thioester **10**. Yield: 98%; mp: 50.8–51.0°C ($CHCl_3$, hexane); IR (KBr): 2927, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): δ=7.68 (s, 1H, H-4), 4.11 (s, 2H, CH_2S), 2.36 (s, 3H, CH_3CO), 2.34 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=194.4 (CO), 148.6 (C-6), 146.6 (C-2), 142.2 (C-4), 131.6 (C-5), 131.3 (C-3), 30.1 (CH_3),

29.9 (CH_2), 18.6 (CH_3); MS [*m/z* (%)] CI: 250 (100) MH^+, 214 (21) MH^+-HCl, 174 (20) MH^+-CH_3COSH; HRMS: calcd for $C_9H_9Cl_2NSO$: 248.9782, found: 248.9786; CHN analysis: calcd for $C_9H_9Cl_2NSO$: C 43.21, H 3.63, N 5.60; found: C 43.36, H 3.49, N 5.52.

4.2. General procedure for the synthesis of thioethers 12

To a stirred solution of 6.6 g of thioester **10** in 200 mL of MeOH was added 1.71 g (1.2 equiv.) of NaOMe under a nitrogen atmosphere. After reaction at room temperature for 15 min, 1.2 equiv. of electrophile was added, and the reaction allowed to proceed for 1 h. Water (200 mL) was added followed by extraction with CH_2Cl_2 (3×100 mL). The combined extracts were dried over $MgSO_4$ and evaporated. The products were purified by column chromatography before spectral characterisation.

4.2.1. Methyl-2-{[(2,6-dichloro-5-methyl-3-pyridyl)-methyl]-sulfanyl}-acetate (12a). (A). General procedure (electrophile=$ClCH_2COOCH_3$). (B) To an ice-cooled solution of 38 g of bromide **8** and 16.29 mL (1.2 equiv.) of methyl thioglycolate was added 61.1 mL (3 equiv.) of NEt_3 dropwise. After being stirred at room temperature for 30 min under an inert atmosphere, the reaction mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (CH_2Cl_2) to afford thioether **12a**. Yield: (A) 95%, (B) 88%; mp 34.0–35.1°C ($CHCl_3$, hexane); IR (KBr): 2953, 1736 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.65 (s, 1H, H-4), 3.89 (s, 2H, CH_2CO), 3.74 (s, 3H, CH_3O), 3.16 (s, 2H, CH_2S), 2.37 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=170.2 (CO), 148.7 (C-6), 146.9 (C-2), 142.1 (C-4),131.5 (C-5), 130.5 (C-3), 52.4 (CH_3O), 32.5 (CH_2), 32.5 (CH_2), 18.7 (CH_3); MS [*m/z* (%)] CI: 280 (100) MH^+, 244 (19) MH^+-HCl, 174 (24) $MH^+-HSCH_2COOCH_3$; HRMS: calcd for $C_{10}H_{11}Cl_2NO_2S$: 278.9888, found: 278.9884.

4.2.2. 2-{[2,6-Dichloro-5-methyl-3-pyridyl)methyl] sulfanyl}acetonitrile (12b). Electrophile=$BrCH_2CN$; chromatographic purification: EtOAc 30–hexane 70; yield 95%; mp: 53.8–54.6°C ($CHCl_3$, hexane); IR (KBr): 2966, 2920, 2239 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.62 (s, 1H, H-4), 3.99 (s, 2H, CH_2S), 3.29 (s, 2H, CH_2CN), 2.38 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=151.6 (C-6), 148.4 (C-2), 147.4 (C-4),130.4 (C-5), 123.6 (C-3), 115.8 (CN), 33.7 (CH_2), 25.3 (CH_2), 16.9 (CH_3); MS [*m/z* (%)] CI: 247 (100) MH^+, 211 (3) MH^+-HCl; HRMS: calcd for $C_9H_9Cl_2NSO$: 245.9779, found: 245.9785; CHN analysis: calcd for $C_9H_9Cl_2NSO$: C 43.74, H 3.26, N 11.33; found: C 43.45, H 3.13, N 11.25.

4.2.3. 3-[(Benzylsulfanyl)methyl]-2,6-dichloro-5-methyl-pyridine (12c). Electrophile=benzyl bromide; chromatographic purification: EtOAc 20–hexane 80; yield: 75%; mp: 44.5–45.0°C ($CHCl_3$, hexane); IR (KBr): 3025, 2907 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.41 (s, 1H, H-4), 7.41 (m, 5H, H-arom), 3.69 (s, 2H, CH_2S), 3.64 (s, 2H, CH_2Ph), 2.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 148.2 (C-2), 146.5 (C-6), 141.8 (C-4), 137.0 (C-*ipso*), 131.4 (C-3), 130.3 (C-5), 128.4 (C-*o*), 128.2 (C-*m*), 127.1 (C-*p*), 36.5 (CH_2S), 31.8 (CH_2Ph), 18.6 (CH_3–pyr); MS [*m/z* (%)] EI: 297 (21) $M^{+\cdot}$, 262 (5) $M^{+\cdot}-Cl$, 206 (7) $M^{+\cdot}-Bn$, 174 (11) $M^{+\cdot}-BnS$, 91 (100) Bn^+; HRMS: calcd for $C_{14}H_{13}Cl_2NS$: 297.0146, found: 297.0152.

4.2.4. Synthesis of methyl 2-{[(2,6-dichloro-5-methyl-3-pyridyl)methyl]sulfonyl}acetate (6a). To a stirred solution of 3 g of thioether **12a** in 50 mL of CH_2Cl_2 was added 7.5 g (3 equiv.) of *m*CPBA (70–75% in water). After reaction for 5 h at room temperature under an inert atmosphere, 15 mL of a saturated $NaHCO_3$ solution was added. After further reaction for 20 min, the organic layer was separated and the water layer extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (CH_2Cl_2) to afford sulfone **6a**. Yield: 87%; mp: 108.5–109.5°C ($CHCl_3$, hexane); IR (KBr): 2976–2919, 1741, 1308, 1126 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.79 (s, 1H, H-4), 4.71 (s, 2H, CH_2SO_2), 4.04 (s, 2H, CH_2CO), 3.86 (s, 3H, CH_3O), 2.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=170.6 (CO), 149.5 (C-6), 149.3 (C-2), 144.1 (C-4), 132.4 (C-5), 121.2 (C-3), 57.1 (CH_2CO), 56.7 (CH_2SO_2), 53.6 (CH_3O), 18.8 (CH_3); MS [*m/z* (%)] CI: 312 (100) MH^+, 276 (5) MH^+-HCl; HRMS: calcd for $C_{10}H_{11}Cl_2NO_4S$: 310.9785, found: 310.9781.

4.3. General procedure for the synthesis of dihydrothieno[3,4-*b*]pyridines 13 and 14

A solution of 1.8 mmol of thioether **12a**,**b** in 10 mL of THF was added slowly to a suspension of 0.43 g (2 equiv.) of KH in 50 mL of THF. After being stirred at room temperature for 10 min under argon, the deep red solution was cooled to −78°C (acetone–CO_2) and treated with saturated aq. NH_4Cl. The mixture was then brought to room temperature and extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (EtOAc 30–hexane 70) to afford **13** or **14**.

4.3.1. Methyl 2-chloro-3-methyl-5,7-dihydrothieno[3,4-*b*]pyridine-7-carboxylate (13). Yield: 88%; mp: yellow oil; IR (NaCl): 2953, 1737 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.49 (s, 1H, H-4), 5.02 (s, 1H, H-7), 4.38 (d, ^2J=15.0 Hz, 1H, H-5), 4.05 (d, ^2J=15.0 Hz, 1H, H-5), 3.74 (s, 3H, CH_3O), 2.37 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=171.6 (CO), 156.2 (C-7a), 151.1 (C-2), 136.1 (C-4), 133.8 (C-3), 132.5 (C-4a), 52.8 (C-7), 52.7 (CH_3O), 34.2 (C-5), 19.5 (CH_3); MS [*m/z* (%)] CI: 244 (100) MH^+, 208 (3) MH^+-HCl, 184 (41) $MH^+-HCOOCH_3$; HRMS: calcd for $C_{10}H_{11}ClNO_2S$: 244.0199, found: 244.0208.

4.3.2. 2-Chloro-3-methyl-5,7-dihydrothieno[3,4-*b*]pyridine-7-carbonitrile (14). Yield: 80%; mp: 134.9–135.1°C ($CHCl_3$/hexane); IR (KBr): 2953, 1737 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.54 (s, 1H, H-4), 5.25 (d, 1H, ^4J=2.7 Hz, H-7), 4.42 (dd, 1H, ^2J=14.2 Hz, ^4J=2.7 Hz, H-5), 4.28 (d, 1H, ^2J=14.2 Hz, H-5), 2.42 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=152.3 (C-7a), 152.3 (C-2), 136.3 (C-4), 132.6 (C-4a), 132.3 (C-3), 117.5 (CN), 38.7 (C-7), 34.0 (C-5), 19.6 (CH_3); MS [*m/z* (%)] CI:221 (24) MH^+, 184 (100) MH^+-HCN; HRMS: calcd for $C_9H_7ClN_2S$: 210.0019, found: 210.0013.

4.4. General procedure for the synthesis of 5,7-dihydro thieno[3,4-*b*]pyridines 15a–c and 16a,b

A solution of 1 mmol of thioether **12a**,**b** in 10 mL of THF was added dropwise to a suspension of 0.25 g (2 equiv.) of KH in 50 mL of THF under an inert atmosphere. The reaction mixture was stirred for 10–30 min until the solution coloured dark red. Then, 1.2 equiv. of electrophile was slowly added and stirring was continued for 10 min. The mixture was cooled to −78°C (acetone–CO_2) and saturated NH_4Cl solution was added. The reaction mixture was brought to room temperature and extracted with CH_2Cl_2 (3×50 mL); the organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (EtOAc 30–hexane 70) to afford thienopyridines **15a**–**c** and **16a**,**b**.

4.4.1. Methyl 2-chloro-3,7-dimethyl-5,7-dihydrothieno[3,4-*b*]pyridine-7-carboxylate (15a). Electrophile=methyl iodide; yield: 90%; mp: 142.5–142.9°C ($CHCl_3$, hexane); IR (KBr): 2929, 1737 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.46 (s, 1H, H-4), 4.29 (d, 1H, ^2J=16.0 Hz, H-5), 4.01 (d, 1H, ^2J=16.0 Hz, H-5), 3.67 (s, 3H, CH_3O), 2.38 (s, 3H, CH_3–pyr), 1.92 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=172.4 (CO), 159.0 (C-2), 150.5 (C-7a), 135.1 (C-4), 133.4 (C-3), 130.0 (C-4a), 59.5 (C-7), 52.3 (CH_3O), 32.5 (C-5), 24.5 (CH_3), 19.3 (CH_3–pyr); MS [*m*/*z* (%)] EI:257 (10) $M^{+\cdot}$, 198 (100) $M^{+\cdot}-COOCH_3$; HRMS: calcd for $C_{11}H_{12}ClNO_2S$: 257.0277, found: 257.0274; CHN analysis: calcd for $C_{11}H_{12}NO_2S$: C 45.60, H 4.17, N 4.83; found: C 45.42, H 3.90, N 4.62.

4.4.2. Dimethyl 2-chloro-3-methyl-thieno[3,4-*b*]pyridine-7,7(5*H*)-dicarboxylate (15b). Electrophile=$ClCO_2CH_3$; yield: 83%; mp: 163.0–164.0°C ($CHCl_3$, hexane); IR (KBr): 2957, 1762, 1732 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.03 (s, 1H, H-4), 4.24 (s, 2H, H-5), 3.81 (s, 6H, CH_3O), 2.38 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=167.9 (CO), 153.6 (C-2), 150.7 (C-7a), 135.9 (C-4), 133.6 (C-3), 132.0 (C-4a), 68.7 (C-7), 53.5 (CH_3O), 32.9 (C-5), 19.3 (CH_3); MS [*m*/*z* (%)] CI: 302 (100) MH^+, 242 (23) $MH^+-HCOOCH_3$, 266 (9) MH^+-HCl; HRMS: calcd for $C_{12}H_{12}ClNO_4S$: 301.0176, found: 301.0783.

4.4.3. Methyl 7-benzyl-2-chloro-3-methyl-5,7-dihydrothieno[3,4-*b*]pyridine-7-carboxylate (15c). Electrophile=BnBr; yield: 77%; mp: 134.0–134.5°C ($CHCl_3$, hexane); IR (KBr): 3020, 1733 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.18 (s, 1H, H-4), 7.08 (m, 5H, H-Ph), 3.90 (d, 1H, ^2J=14.0 Hz, H-5), 3.71 (d, 1H, ^2J=14.0 Hz, H-5), 3.70 (s, 3H, CH_3O), 3.53 (d, 1H, ^2J=14.0 Hz, CH_2–Ph), 3.41 (d, 1H, ^2J=14.0 Hz, CH_2–Ph), 2.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=172.8 (CO), 158.1 (C-2), 150.3 (C-7a), 135.7 (C-4), 134.5 (C-3), 131.2 (C-*ipso*), 130.7 (C-*m*), 127.4 (C-*o*), 126.6 (C-*p*), 126.5 (C-4a), 66.7 (C-7), 53.1 (CH_3O), 41.9 (CH_2–Ph), 32.8 (C-5), 19.6 (CH_3); MS [*m*/*z* (%)] CI: 334 (100) MH^+, 298 (10) MH^+-HCl, 274 (21) $MH^+-HCOOCH_3$, 242 (22) MH^+-BnH; HRMS: calcd for $C_{17}H_{16}ClNO_2S$: 333.0590, found: 333.0588.

4.4.4. 2-Chloro-3,7-dimethyl-5,7-dihydrothieno[3,4-*b*]-pyridine-7-carbonitrile (16a). Electrophile=methyl iodide; yield: 85%; mp: 102.0–102.3°C ($CHCl_3$, hexane); IR (KBr): 2975, 2360 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.53 (s, 1H, H-4), 4.36 (d, 1H, ^2J=14.3 Hz, H-5), 4.13 (d, 1H, ^2J=14.3 Hz, H-5), 2.41 (s, 3H, CH_3–pyr), 2.06 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=156.2 (C-2), 151.5 (C-7a), 136.4 (C-4), 132.4 (C-3), 131.8 (C-4a), 120.6 (CN), 48.6 (C-7), 32.5 (C-5), 27.8 (CH_3), 19.5 (CH_3–pyr); MS [*m*/*z* (%)] CI: 225 (100) MH^+, 198 (25) MH^+-HCN; HRMS: calcd for $C_{10}H_9ClN_2S$: 224.0175, found: 224.0176.

4.4.5. Methyl 2-chloro-7-cyano-3-methyl-5,7-dihydrothieno[3,4-*b*]pyridine-7-carboxylate (16b). Electrophile=$ClCO_2CH_3$; yield: 65%; mp: 137.8–138.5°C ($CHCl_3$, hexane); IR (KBr): 2961, 2364, 1739 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.58 (s, 1H, H-4), 4.43 (d, 1H, ^2J=14.0 Hz, H-5), 4.31 (d, 1H, ^2J=14.0 Hz, H-5), 3.85 (s, 3H, CH_3O), 2.41 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=166.4 (CO), 152.2 (C-2), 151.7 (C-7a), 136.3 (C-4), 133.3 (C-3), 132.6 (C-4a), 115.7 (CN), 55.1 (C-7), 54.0 (CH_3O), 34.3 (C-5), 19.5 (CH_3–pyr); MS [*m*/*z* (%)] CI: 269 (70) MH^+, 242 (100) MH^+-HCN, 209 (8) $MH^+-HCOOCH_3$; HRMS: calcd for $C_{11}H_9ClN_2O_2S$: 268.0073, found: 268.0071.

4.5. General procedure for the synthesis of thienopyridines 17a,b and thienopyridinone 18

To a stirred solution of 4.9 mmol of thienopyridine **13**, **14** in 25 mL of CH_2Cl_2 was added 3.43 g (3 equiv.) of *m*CPBA (70–75% in water). After reaction for 3 h at room temperature under an inert atmosphere, 15 mL of a saturated $NaHCO_3$ solution was added and stirring was continued for 20 min. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (EtOAc 30–hexane 70) to afford thienopyridines **17a**,**b** and thienopyridinone **18**.

4.5.1. Methyl 2-chloro-3-methyl-thieno[3,4-*b*]pyridine-7-carboxylate (17a). Yield: 80%; mp: 180–181°C ($CHCl_3$, hexane); IR (KBr): 3100, 2958, 1680, 1606 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.90 (s, 1H, H-5), 7.76 (s, 1H, H-4), 4.00 (s, 3H, CH_3O), 2.45 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=162.0 (CO), 156.8 (C-2), 147.9 (C-7a), 131.8 (C-3), 131.2 (C-4), 124.0 (C-5), 121.7 (C-4a), 115.5 (C-7), 52.4 (CH_3O), 20.5 (CH_3); MS [*m*/*z* (%)] CI: 242 (100) MH^+, 210 (66) MH^+-CH_3OH, 206 (32) MH^+-HCl; HRMS: calcd for $C_{10}H_8ClNO_2S$: 240.9964, found: 240.9974.

4.5.2. 2-Chloro-3-methyl-thieno[3,4-*b*]pyridine-7-carbonitrile (17b). Yield: 57%; mp: 207.0–208.0°C ($CHCl_3$, hexane); IR (KBr): 3052, 2209 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.94 (s, 1H, H-5), 7.83 (s, 1H, H-4), 2.48 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=157.2 (C-2), 152.2 (C-7a), 129.8 (C-4), 129.7 (C-3), 124.1 (C-5), 119.4 (C-4a), 112.7 (CN), 97.0 (C-7), 20.3 (CH_3); MS [*m*/*z* (%)] CI: 209 (100) MH^+, 173 (6) MH^+-HCl; HRMS: calcd for $C_9H_5ClN_2S$: 207.9862, found: 207.9865.

4.5.3. Methyl 3-methyl-2-oxo-1,2-dihydrothieno[3,4-*b*]-pyridine-7-carboxylate (18). Yield: 15%; mp: 192.0–193.0°C (CH_3Cl, hexane); IR (KBr): 3400, 3053, 2952, 1665 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=9.95 (s, 1H, NH),

7.53 (s, 1H, H-5), 7.41 (s, 1H, H-4), 3.82 (s, 3H, CH_3O), 2.17 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=163.2 (CON), 162.8 (CO), 142.4 (C-7a), 131.0 (C-3), 130.1 (C-4), 129.7 (C-4a), 125.9 (C-5), 104.9 (C-7), 52.4 (CH_3O), 17.2 (CH_3); MS [*m*/*z* (%)] CI: 224 (100) MH^+, 192 (37) MH^+-CH_3OH; HRMS: calcd for $C_{10}H_9NO_3S$: 223.0303, found: 223.0306; CHN analysis: calcd for $C_{10}H_9NO_3S$: C 53.80, H 4.06, N 6.27; found: C 53.07, H 3.94, N 6.11.

4.6. General procedure for the synthesis of 6,6-dioxo-6,7-dihydrothieno[3,4-*b*]pyridines 3a,c–f

To a stirred solution of 11.7 mmol of thienopyridine **15a–c**, **16a**,**b** in 200 mL of CH_2Cl_2 was added 13.5 g (3 equiv.) of *m*CPBA (70–75% in water). After reaction at room temperature for 3 h under an inert atmosphere, a saturated $NaHCO_3$ solution was added and stirring was continued for 20 min. The reaction mixture was then extracted with CH_2Cl_2 (3×100 mL); the organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography to afford pyridine sulfolene **3a**,**c–f**.

4.6.1. Methyl 2-chloro-3,7-dimethyl-6,6-dioxo-6,7-dihydro-5*H*-6λ^6-thieno[3,4-*b*pyridine-7-carboxylate (3a). Chromatographic purification: EtOAc 30–hexane 70; yield: 93%; mp: 142.5–143.1°C ($CHCl_3$, hexane); IR (KBr): 3001, 2949, 1750, 1321, 1145 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.59 (s, 1H, H-4), 4.60 (d, 1H, ^2J=15.0 Hz, H-5), 4.34 (d, 1H, ^2J=15.0 Hz, H-5), 3.76 (s, 3H, CH_3O), 2.42 (s, 3H, CH_3–pyr), 1.92 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=166.5 (CO), 152.9 (C-2), 152.2 (C-7a), 136.9 (C-4), 134.2 (C-3), 128.1 (C-4a), 72.9 (C-7), 52.9 (CH_3O), 54.6 (C-5), 19.8 (CH_3–pyr), 13.8 (CH_3); MS [*m*/*z* (%)] CI: 290 (100) MH^+, 254 (3) MH^+-HCl, 226 (30) MH^+-SO_2; HRMS: calcd for $C_{11}H_{12}ClNO_4S$: 289.0176, found: 289.0175.

4.6.2. Dimethyl 2-chloro-3-methyl-6,6-dioxo-5,6-dihydro-7*H*-6λ^6-thieno[3,4-*b*]pyridine-7,7-dicarboxylate (3c). Chromatographic purification: EtOAc 35–Hex 75; yield: 82%; mp: 175.1–175.8°C ($CHCl_3$, hexane); IR (KBr): 2960, 1738, 1354, 1163 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.57 (s, 1H, H-4), 4.57 (s, 2H, H-5), 3.90 (s, 6H, CH_3O), 2.43 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=161.6 (CO), 152.5 (C-2), 148.1 (C-7a), 136.5 (C-4), 135.1 (C-3), 126.5 (C-4a), 79.3 (C-7), 55.3 (C-5), 54.1 (CH_3O), 19.8 (CH_3); MS [*m*/*z* (%)] CI: 334 (100) MH^+, 298 (6) MH^+-HCl, 270 (16) MH^+-SO_2, 238 (5) MH^+-CH_3OH, $-SO_2$; HRMS: calcd for $C_{12}H_{12}ClNO_6S$: 333.0074, found: 333.0079; CHN analysis: calcd for $C_{12}H_{12}ClNO_6S$: C 43.19, H 3.62, N 4.20; found: C 43.38, H 3.53, N 4.12.

4.6.3. Methyl 7-benzyl-2-chloro-3-methyl-6,6-dioxo-6,7-dihydro-5*H*-6λ^6-thieno[3,4-*b*]pyridine-7-carboxylate (3d). Chromatographic purification: EtOAc 20–Hex 80; yield: 80%; mp: 132.0–133.1°C ($CHCl_3$, hexane); IR (KBr): 3020, 2962, 1714, 1365, 1135 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.30 (s, 1H, H-4), 7.13 (m, 5H, H-Ph), 4.27 (d, 1H, ^2J=15.0 Hz, H-5), 3.97 (d, 1H, ^2J=15.0 Hz, H-5), 3.81 (s, 3H, CH_3O), 3.63 (d, 1H, ^2J=14.0 Hz, CH_2–Ph), 3.58 (d, 1H, ^2J=14.0 Hz, CH_2–Ph), 2.37 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=164.9 (CO), 151.9 (C-2), 151.3 (C-7a), 136.2 (C-4), 133.8 (C-3), 133.1 (C-*ipso*), 131.0 (C-*m*), 127.8 (C-*o*), 127.2 (C-*p*), 125.7 (C-4a), 76.9 (C-7), 54.8 (C-5), 53.6 (CH_3O), 38.2 (CH_2–Ph), 19.6 (CH_3); MS [*m*/*z* (%)] CI: 322 (100) MH^+, 258 (17) MH^+-SO_2; HRMS: calcd for $C_{16}H_{16}ClNO_4S$: 321.0590, found: 321.0589.

4.6.4. 2-Chloro-3,7-dimethyl-6,6-dioxo-6,7-dihydro-5*H*-6λ^6-thieno[3,4-*b*]pyridine-7-carbonitrile (3e). Chromatographic purification: CH_2Cl_2 98–EtOAc 2; yield: 94%; mp: 165.4–166.3°C ($CHCl_3$, hexane); IR (KBr): 2983, 2243, 1351, 1141 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.59 (s, 1H, H-4), 4.59 (d, 1H, ^2J=15.8 Hz, H-5), 4.43 (d, 1H, ^2J=15.8 Hz, H-5), 2.46 (s, 3H, CH_3–pyr), 2.05 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=153.6 (C-2), 149.2 (C-7a), 137.2 (C-4), 136.0 (C-3), 124.2 (C-4a), 114.3 (CN), 61.2 (C-7), 53.8 (C-5), 19.9 (CH_3), 17.6 (CH_3–pyr); MS [*m*/*z* (%)] CI: 257 (100) MH^+, 230 (4) MH^+-HCN, 221 (11) MH^+-HCl, 193 (48) MH^+-SO_2; HRMS: calcd for $C_{10}H_9ClN_2SO_2$: 256.0073, found: 256.0071; CHN analysis: calcd for $C_{10}H_9ClN_2O_2S$: C 46.79, H 3.53, N 10.91; found: C 46.86, H 3.33, N 10.77.

4.6.5. Methyl 2-chloro-7-cyano-3-methyl-6,6-dioxo-6,7-dihydro-5*H*-6λ^6-thieno[3,4-*b*]pyridine-7-carboxylate (3f). Chromatographic purification: CH_2Cl_2 95–EtOAc 5; yield: 62%; mp: white foam; IR (NaCl): 2934, 2362, 1757, 1358, 1147 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.63 (s, 1H, H-4), 4.70 (d, 1H, ^2J=15.3 Hz, H-5), 4.62 (d, 1H, ^2J=15.3 Hz, H-5), 3.97 (s, 3H, CH_3O), 2.48 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=160.8 (CO), 153.5 (C-2), 146.4 (C-7a), 137.1 (C-4), 136.9 (C-3), 125.6 (C-4a), 109.0 (CN), 71.3 (C-7), 56.1 (C-5), 55.6 (CH_3O), 20.0 (CH_3–pyr); MS [*m*/*z* (%)] CI: 301 (30) MH^+, 265 (9) MH^+-HCl, 209 (100) MH^+-SO_2; HRMS: calcd for $C_{11}H_9ClN_2O_4S$: 299.9971, found: 299.9965.

4.6.6. Methyl 2-chloro-3-methyl-6,6-dioxo-6,7-dihydro-5*H*-6λ^6-thieno[3,4-*b*]pyridine-7-carboxylate (3b). To a stirred solution of 2 g of pyridine sulfolene **3c** in 40 mL of MeOH was added 1.2 g (1.5 equiv.) of NaOMe. After reaction at reflux temperature for 2 h under an inert atmosphere, the reaction mixture was cooled to room temperature and neutralised with 20 mL of a saturated NH_4Cl solution. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (EtOAc 50–Hex 50) to afford pyridine sulfolene **3b**. Yield: 85%; mp: 117.9–118.4°C ($CHCl_3$, hexane); IR (KBr): 2926, 1734, 1324, 1111 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.58 (s, 1H, H-4), 5.12 (s, 1H, H-7), 4.53 (d, 1H, ^2J=15.0 Hz, H-5), 4.39 (d, 1H, ^2J=15.0 Hz, H-5), 3.85 (s, 3H, CH_3O), 2.43 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=163.9 (CO), 152.4 (C-2), 145.5 (C-7a), 136.8 (C-4), 134.6 (C-3), 126.6 (C-4a), 70.8 (C-7), 56.1 (C-5), 53.8 (CH_3O), 19.7 (CH_3); MS [*m*/*z* (%)] EI: 275 (28) $M^{+\cdot}$, 211 (100) $M^{+\cdot}-SO_2$, 180 (59) $M^{+\cdot}-SO_2-OCH_3$, 152 (43) $M^{+\cdot}-SO_2-COOCH_3$; HRMS: calcd for $C_{10}H_{11}ClNO_2S$: 275.0019, found: 275.0019.

4.7. General procedure for thermolysis in absence of a dienophile

A solution of 200 mg of pyridine sulfolene **3a**,**c**,**e** in 5 mL of

o-dichlorobenzene was subjected to three freeze–pump–thaw cycles. The glass tube was sealed and heated under the conditions specified below. The *o*-dichlorobenzene solvent was removed by Kugelrohr distillation. The residue was purified by column chromatography (CH_2Cl_2) to afford products **19**–**21**.

4.7.1. Methyl 2-(6-chloro-3,5-dimethyl-2-pyridyl) acrylate (19). Reaction conditions: 200°C, 12 h; yield: 78%; mp: yellow oil; IR (NaCl): 2954, 1725 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.38 (s, 1H, H-4), 6.63 (s, 1H, CH═), 5.93 (s, 1H, CH═), 3.77 (s, 3H, CH_3O), 2.35 (s, 3H, CH_3–pyr), 2.16 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$/TMS): δ=165.9 (CO),152.3 (C-2), 146.6 (C-4), 142.2 (C═),131.6 (C-6), 131.3 (CH_2), 130.7 (C-3), 130.7 (C-5), 52.1 (CH_3O), 19.0 (CH_3), 17.9 (CH_3); MS [*m*/*z* (%)] CI: 226 (100) MH^+; 190 (30) MH^+-HCl.

4.7.2. Methyl 2-chloro-7-methoxy-3-methyl-5*H*-pyrano [3,4-*b*]pyridine-8-carboxylate (20). Reaction conditions: 160°C, 30 min; yield: 75%; mp: 147.5–148.0°C ($CHCl_3$, hexane); IR (KBr): 2947, 1687 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.13 (s, 1H, H-4), 5.19 (s, 2H, H-5), 3.95 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 2.29 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=170.5 (C-7), 165.1 (CO), 151.0 (C-8a), 148.5 (C-2), 134.2 (C-4), 127.2 (C-4a), 118.2 (C-3), 88.0 (C-8), 68.5 (C-5), 56.2 (CH_3O), 51.2 (CH_3O), 19.2 (CH_3–pyr); MS [*m*/*z* (%)] CI: 270 (72) MH^+, 238 (100) MH^+-CH_3OH, 234 (30) MH^+-HCl.

4.7.3. 2-Chloro-7-methoxy-3-methyl-5*H*-pyrano[3,4-*b*]-pyridine-8-carbonitrile (21). Reaction conditions: 200°C, 12 h; yield: 80%; mp: 188.5–189.0°C ($CHCl_3$, hexane); IR (KBr): 2922, 2219, 1604 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.14 (s, 1H, H-4), 5.38 (s, 2H, H-5), 3.99 (s, 3H, CH_3O), 2.31 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ= 170.3 (C-7), 151.6 (C-8a), 147.2 (C-2), 134.2 (C-4), 128.2 (C-4a), 116.1 (C-3), 114.2 (CN), 76.9 (C-8), 68.5 (C-5), 56.5 (CH_3O), 19.3 (CH_3–pyr); MS [*m*/*z* (%)] CI: 237 (90) MH^+, 205 (100) MH^+-CH_3OH, 201 (26) MH^+-HCl.

4.8. General procedure for intermolecular Diels–Alder reactions

A solution of 150 mg of pyridine sulfolene **3a**–**d** and 5 equiv. of dienophile in 10 mL of dichlorobenzene was subjected to three freeze–pump–thaw cycles. The glass tube was sealed and heated at 200°C for 15 h. The dichlorobenzene solvent was removed by Kugelrohr distillation. The residue was purified by column chromatography (CH_2Cl_2) to afford adducts **22**–**33**.

4.8.1. Methyl (5a*R,8a*R**,9*S**)-2-chloro-3-methyl-6,8-dioxo-7-phenyl-5a,6,7,8,8a,9-hexahydro-5*H*-pyrrolo[3,4-*g*]quinoline-9-carboxylate (22).** Yield: 88%; mp: 160.5–161.0°C ($CHCl_3$, hexane); IR (KBr): 3020, 2974, 1735, 1711 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.34 (m, 3H, H-*m*, H-*p*), 7.31 (s, 1H, H-4), 6.94 (dd, 2H, ^3J=6.4 Hz, ^4J=1.4 Hz, H-*o*), 4.11 (d, 1H, ^3J=8.9 Hz, H-8a), 3.68 (s, 3H, CH_3O), 3.58 (ddd, 1H, ^3J=2.8, 7.9, 8.9 Hz, H-5a), 3.24 (dd, 1H, ^2J=15.8 Hz, ^3J=2.8 Hz, H-5), 2.76 (dd, 1H, ^2J=15.8 Hz, ^3J=7.9 Hz, H-5), 2.33 (s, 3H, CH_3–pyr), 1.99 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=177.5 (C-6), 174.9 (C-8), 174.9 (CO), 150.8 (C-9a), 150.1 (C-2), 139.3 (C-4), 132.0 (C-*ipso*), 131.5 (C-4a), 129.0 (C-*m*), 128.7 (C-*p*), 127.1 (C-3), 126.3 (C-*o*), 53.3 (CH_3O), 51.2 (C-9), 46.6 (C-8a), 39.6 (C-5a), 28.1 (C-5), 19.6 (CH_3), 19.3 (CH_3–pyr); MS [*m*/*z* (%)] CI: 399 (90) MH^+, 341 (40) $MH^+-COOCH_3$; HRMS: calcd for $C_{21}H_{19}ClN_2O_4$: 398.1033, found: 398.1032.

4.8.2. Dimethyl (5a*R,8a*R**)-2-chloro-3-methyl-6,8-dioxo-7-phenyl-5a,6,7,8,8a,9-hexahydro-5*H*-pyrrolo[3,4-*g*]quinoline-9,9-dicarboxylate (23).** Yield: 85%; mp: 222.5–223.0°C ($CHCl_3$, hexane); IR (KBr): 3012, 2957, 1720, 1702 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.41 (m, 6H, H-Ph; H-4), 3.96 (s, 3H, CH_3O), 3.75 (d, 1H, ^3J=8.7 Hz, H-8a), 3.68 (s, 3H, CH_3O), 3.45 (m, 3H, H-5; H-5a), 2.39 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=176.9 (C-6), 174.5 (C-8), 168.1 (CO), 167.8 (CO), 151.8 (C-9a), 151.7 (C-2), 139.3 (C-4), 132.7 (C-*ipso*), 132.2 (C-4a), 129.4 (C-3), 129.1 (C-*m*), 128.6 (C-*p*), 126.6 (C-*o*), 63.7 (C-9), 53.8 (2×CH_3O), 46.2 (C-8a), 38.3 (C-5a), 26.4 (C-5), 19.4 (CH_3–pyr); MS [*m*/*z* (%)] CI: 443 (100) MH^+, 407 (12) MH^+-HCl; HRMS: calcd for $C_{22}H_{19}ClN_2O_6$: 442.0932, found: 442.0925.

4.8.3. (5a*R,8a*R**,9*S**)-2-Chloro-3,9-dimethyl-6,8-dioxo-7-phenyl-5a,6,7,8,8a,9-hexahydro-5*H*-pyrrolo[3,4-*g*]-quinoline-9-carbonitrile (24).** Yield: 65%; mp: 240.0–241.0°C ($CHCl_3$, hexane); IR (KBr): 3018, 2973, 2289, 1712, 1695 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.46 (s, 1H, H-4), 7.36 (m, 3H, H-*m*, H-*p*), 6.93 (dt, 2H, ^3J=6.4 Hz, ^4J=1.4 Hz, H-*o*), 3.78 (d, 1H, ^3J=9.2 Hz, H-8a), 3.70 (ddd, 1H, ^3J=2.0, 7.4, 9.2 Hz, H-5a), 3.58 (dd, 1H, ^2J=15.9 Hz, ^3J=7.4 Hz, H-5), 3.44 (dd, 1H, ^2J=15.9 Hz, ^3J=2.0 Hz, H-5), 2.39 (s, 3H, CH_3), 2.17 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=176.3 (2×CO), 172.1 (C-9a), 150.5 (CN), 148.9 (C-2), 139.9 (C-4), 131.0 (C-*ipso*), 132.2 (C-4a), 129.4 (C-3), 129.1 (C-*m*), 128.6 (C-*p*), 126.6 (C-*o*), 63.7 (C-9), 53.8 (2×CH_3O), 46.2 (C-8a), 38.3 (C-5a), 26.4 (C-5), 19.4 (CH_3–pyr); MS [*m*/*z* (%)] CI: 366 (100) MH^+, 339 (15) MH^+-HCN, 330 (13) MH^+-HCl; HRMS: calcd for $C_{20}H_{16}ClN_3O_2$: 365.0931, found: 365.0936.

4.8.4. Trimethyl (6*R,7*R**,8*S**)-2-chloro-3,8-dimethyl-5,6,7,8-tetrahydro-6,7,8-quinoline tricarboxylate (25).** Yield: 61%; mp: yellow foam; IR (NaCl): 2984, 1741–1725 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.29 (s, 1H, H-4), 3.74 (s, 3H, CH_3O), 3.67 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 3.38 (dd, 1H, ^2J=17.2 Hz, ^3J=11.5 Hz, H-5), 3.73 (d, 1H, ^3J=3.9 Hz, H-7), 3.16 (ddd, 1H, ^3J=11.5, 6.5, 3.9 Hz, H-6), 3.02 (dd, 1H, ^2J=17.2 Hz, ^3J=6.5 Hz, H-5), 2.33 (s, 3H, CH_3–pyr), 1.70 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ=174.7 (CO), 173.0 (CO), 171.1 (CO), 151.9 (C-8a), 148.8 (C-2), 139.5 (C-4), 130.9 (C-3), 129.4 (C-4a), 53.0 (CH_3O), 52.2 (CH_3O), 51.7 (CH_3O), 50.6 (C-8), 48.2 (C-6), 38.8 (C-7), 27.2 (C-5), 21.5 (CH_3), 19.4 (CH_3–pyr); MS [*m*/*z* (%)] CI: 370 (100) MH^+, 334 (15) MH^+-HCl, 310 (9) $MH^+-HCOOCH_3$; HRMS: calcd for $C_{17}H_{20}ClNO_6$: 369.0979, found: 369.0985.

4.8.5. Trimethyl (6R*,7R*,8R*)-2-chloro-3-methyl-5,6,7,8-tetrahydro-6,7,8-quinoline- tricarboxylate (26). Yield: 73%; mp: yellow foam; IR (NaCl): 2956, 1723 cm^{-1}; ^1H NMR ($CDCl_3$/TMS): δ=7.32 (s, 1H, H-4),

4.44 (d, 1H, ^3J=4.9 Hz, H-8), 3.79 (s, 3H, CH_3O), 3.74 (dd, 1H, ^3J=3.7, 4.9 Hz, H-7), 3.71 (s, 3H, CH_3O), 3.67 (s, 3H, CH_3O), 3.57 (ddd, 1H, ^3J=3.7, 6.3, 8.4 Hz, H-6), 3.21 (dd, 1H, ^2J=17.4 Hz, ^3J=8.4 Hz, H-5), 3.09 (dd, 1H, ^2J=17.4 Hz, ^3J=6.3 Hz, H-5) 2.33 (s, 3H, CH_3–pyr); ^{13}C NMR ($CDCl_3$): δ=172.7 (CO), 172.4 (CO), 171.3 (CO), 149.2 (C-8a), 148.6 (C-2), 140.3 (C-4), 131.5 (C-4a), 128.8 (C-3), 52.7 (CH_3O), 52.3 (CH_3O), 52.2 (CH_3O), 48.1 (C-7), 43.4 (C-6), 37.8 (C-8), 27.1 (C-5), 19.1 (CH_3–pyr); MS [*m*/*z* (%)] CI: 356 (100) MH^+, 320 (24) MH^+-HCl, 298 (22) MH^+-CH_2O, CO; HRMS: calcd for $C_{16}H_{18}ClNO_6$: 355.0823, found: 355.0826.

4.8.6. Dimethyl (5a*R,8a*R**)-2-chloro-3-methyl-5,5a,6,7,8,8a-hexahydro-9*H*-cyclo-penta[*g*]quinoline-9,9-dicarboxylate (28).** Yield: 60%, mp: yellow oil; IR (NaCl): 2988, 2927, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): δ=7.24 (s, 1H, H-4), 3.80 (s, 1H, CH_3O), 3.72 (s, 3H, CH_3O), 3.07 (dd, 1H, ^2J=15.8 Hz, ^3J=7.5 Hz, H-5), 2.85 (m, 1H, H-8a), 2.56 (m, 1H, H-5a), 2.36 (dd, 1H, ^2J=15.8 Hz, ^3J=5.3 Hz, H-5), 2.32 (s, 3H, CH_3–pyr), 1.87 (m, 2H, H-7), 1.59 (m, 1H, H-6), 1.51 (m, 1H, H-6), 1.25 (m, 2H, H-8); ^{13}C NMR ($CDCl_3$): δ=170.4 (CO), 169.6 (CO), 150.8 (C-9a), 148.7 (C-2), 139.6 (C-4), 131.4 (C-4a), 130.7 (C-3), 63.4 (C-9), 52.9 (CH_3O), 52.5 (CH_3O), 44.9 (C-8a), 34.8 (C-5a), 33.3 5C-5), 31.1 (C-6), 28.4 (C-8), 23.3 (C-7), 19.3 (CH_3–pyr); MS [*m*/*z* (%)] CI: 338 (100) MH^+, 336 (20) MH^+-H_2, 302 (20) MH^+-HCl, 278 (10) $MH^+-HCOOCH_3$.

4.8.7. Methyl (7*R,8*R**)-2-chloro-8-cyano-3,8-dimethyl-5,6,7,8-tetrahydro-7-quinoline-carboxylate (29).** Yield: 70%; mp: yellow foam; IR (NaCl): 2952, 2239, 1738 cm^{-1}; ^{1}H NMR (C_6D_6/TMS): δ=6.35 (s, 1H, H-4), 3.29 (s, 3H, CH_3O), 2.89 (dd, 1H, ^3J=3.3, 10.0 Hz, H-7), 2.13 (ddd, 1H, ^2J=17.0 Hz, ^3J=6.6, 6.6 Hz, H-5), 2.00 (ddd, 1H, ^2J=17.0 Hz, ^3J=6.0, 8.8 Hz, H-5), 1.88 (s, 3H, CH_3–pyr), 1.86 (ddt, 1H, ^2J=14.0 Hz, ^3J=3.3, 6.0, 6.0 Hz, H-6), 1.62 (s, 3H, CH_3), 1.58 (dddd, 1H, ^2J=14.0 Hz, ^3J=6.6, 8.8, 10.0 Hz, H-6); ^{13}C NMR ($CDCl_3$): δ=171.7 (CO), 150.5 (C-8a), 149.3 (C-2), 140.5 (C-4), 132.3 (CN), 129.2 (C-4a), 122.4 (C-3), 52.2 (CH_3O), 47.6 (C-7), 43.4 (C-8), 22.5 (CH_3), 21.0 (C-5), 19.0 (CH_3–pyr); MS [*m*/*z* (%)] CI: 279 (100) MH^+, 252 (16) MH^+-HCN, 219 (4) $MH^+-HCOOCH_3$; HRMS: calcd for $C_{14}H_{15}ClN_2O_2$: 278.0822, found: 278.0820.

4.8.8. Methyl (3a*S,9*R**,9a*R**)-7-chloro-6,9-dimethyl-2,3,3a,4,9,9a-hexahydro-furo[3,2-*g*]quinoline-9-carboxylate (30).** Yield: 55%; mp: 115.2–116.4°C ($CHCl_3$, hexane); IR (KBr): 2925, 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): δ=7.26 (s, 1H, H-5), 4.60 (d, 1H, ^3J=7.8 Hz, H-9a), 3.60 (s, 3H, CH_3O), 3.50 (ddd, 1H, ^3J=3.9, 8.6, 8.6 Hz, H-2), 3.39 (ddd, 1H, ^3J=6.2, 8.6, 8.6 Hz, H-2), 2.93 (m, 1H, H-3a), 2.63 (dd, 1H, ^2J=15.6 Hz, ^3J=7.1 Hz, H-4), 2.48 (dd, 1H, ^2J=15.6 Hz, ^3J=1.9 Hz, H-4), 2.33 (s, 3H, CH_3–pyr), 2.18 (m, 1H, H-3), 1.80 (s, 3H, CH_3), 1.31 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$): δ=174.0 (CO), 154.0 (C-8a), 149.1 (C-7), 139.4 (C-5), 130.6 (C-4a), 130.2 (C-6), 83.4 (C-9a), 77.0 (C-9), 66.8 (C-2), 52.3 (CH_3O), 35.4 (C-3a), 34.4 (C-4), 31.6 (C-3), 19.9 (CH_3), 19.2 (CH_3–pyr); MS [*m*/*z* (%)] EI: 295 (45) $M^{+\cdot}$, 236 (98) $M^{+\cdot}-COOCH_3$, 208 (37) $M^{+\cdot}-COOCH_3-C_2H_4$; HRMS: calcd for: $C_{15}H_{18}ClNO_3$: 295.0975, found: 295.0973.

4.8.9. Methyl (3a*S,9a*R**)-7-chloro-6-methyl-2,3,3a,4,9,9a-hexahydro-furo[3,2-*g*]quinoline-9,9-dicarboxylate (31).** Yield: 75%; mp: yellow foam; IR (NaCl): 2974, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): δ=7.29 (s, 1H, H-5), 4.83 (d, 1H, ^3J=6.8 Hz, H-9a), 3.60 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 3.75 (m, 2H, H-2), 2.88 (m, 1H, H-3a), 2.79 (dd, 1H, ^2J=16.0 Hz, ^3J=7.7 Hz, H-4), 2.54 (dd, ^2J=16.0 Hz, ^3J=5.0 Hz, H-4), 2.39 (s, 3H, CH_3–pyr), 2.18 (dddd, 1H, ^2J=12.2 Hz, ^3J=5.4, 7.2, 7.6 Hz, H-3), 1.31 (dddd, 1H, ^2J=12.2 Hz, ^3J=5.9, 6.9, 7.3 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ=168.0 (CO), 167.4 (CO), 149.5 (C-8a), 148.7 (C-7), 139.0 (C-5), 131.3 (C-4a), 130.5 (C-6), 80.8 (C-9a), 67.2 (C-9), 63.8 (C-2), 52.7 (CH_3O), 52.1 (CH_3O), 35.2 (C-3a), 33.3 (C-4), 30.7 (C-3), 19.0 (CH_3–pyr); MS [*m*/*z* (%)] EI: 339 (50) $M^{+\cdot}$, 280 (100) $M^{+\cdot}-COOCH_3$, 248 (95) $M^{+\cdot}-COOCH_3-CH_3OH$, 221 (18) $M^+-2\times COOCH_3$; HRMS: calcd for $C_{16}H_{18}ClNO_5$: 339.0873, found: 339.0867.

4.8.10. (3a*S,9*S**,9a*R*)-7-Chloro-6,9-dimethyl-2,3,3a,4,9,9a-hexahydrofuro[3,2-*g*]quinoline-9-carbonitrile (32).** Yield: 67%; mp: 79.1–81.0°C ($CHCl_3$, hexane); IR (KBr): 2943, 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): δ=7.35 (s, 1H, H-5), 4.40 (d, 1H, ^3J=7.9 Hz, H-9a), 3.47 (m, 2H, H-2), 3.27 (dd, 1H, ^2J=15.6 Hz, ^3J=7.2 Hz, H-4), 3.04 (m, 1H, H-3a), 2.66 (dd, 1H, ^2J=15.6 Hz, ^3J=1.8 Hz, H-4), 2.36 (s, 3H, CH_3–pyr), 2.21 (m, 1H, H-3), 1.93 (s, 3H, CH_3), 1.36 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$): δ=154.0 (C-8a), 149.4 (CN), 148.6 (C-7), 139.8 (C-5), 132.4 (C-4a), 130.6 (C-6), 83.4 (C-9a), 67.3 (C-2), 40.1 (C-9), 35.4 (C-3a), 34.0 (C-4), 31.0 (C-3), 19.6 (CH_3), 19.2 (CH_3–pyr); MS [*m*/*z* (%)] CI: 263 (100) MH^+, 236 (27) MH^+-HCN, 227 (3) MH^+-HCl; HRMS: calcd for $C_{14}H_{15}ClN_2O$: 262.0873, found: 262.0870.

4.8.11. (7*R,8*S**)-2-Chloro-7-ethoxy-3,8-dimethyl-5,6,7,8-tetrahydro-8-quinolinecarbonitrile (33).** Yield: 63%; mp: yellow foam; IR (NaCl): 2931, 2224 cm^{-1}; ^{1}H NMR ($CDCl_3$/TMS): δ=7.28 (s, 1H, H-4), 3.92 (dd, 1H, ^3J=2.4, 8.0 Hz, H-7), 3.75 (dq, 1H, ^2J=9.3 Hz, ^3J=7.0 Hz, CH_2O), 3.65 (dq, 1H, ^2J=9.3 Hz, ^3J=7.0 Hz, CH_2O), 2.87 (dt, 1H, ^2J=17.1 Hz, ^3J=6.6 Hz, H-5), 2.72 (dt, 1H, ^2J=17.1 Hz, ^3J=6.5 Hz, H-5), 2.33 (s, 3H, CH_3–pyr), 2.15 (m, 1H, H-6), 2.03 (m, 1H, H-6), 1.75 (s, 3H, CH_3), 1.23 (t, 3H, ^3J=7.0 Hz, CH_3CH_2O); ^{13}C NMR ($CDCl_3$): δ=150.7 (C-8a), 149.5 (C-2), 140.2 (C-4), 132.0 (C-4a), 129.5 (C-3), 123.0 (CN), 78.2 (C-7), 65.9 (CH_2O), 43.3 (C-8), 24.1 (C-6), 23.2 (C-5), 21.1 (CH_3), 19.1 (CH_3–pyr), 15.4 (CH_3CH_2O); MS [*m*/*z* (%)] CI: 265 (100) MH^+, 238 (10) MH^+-HCN, 229 (9) MH^+-HCl, 192 (4) $MH^+-HCN-HOCH_2CH_3$; HRMS: calcd for $C_{14}H_{17}ClN_2O$: 264.1029, found: 264.1023.

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