Efficient cleavage of the N–O bond of 3,6-dihydro-1,2-oxazines mediated by some α-hetero substituted carbonyl compounds in mild conditions†

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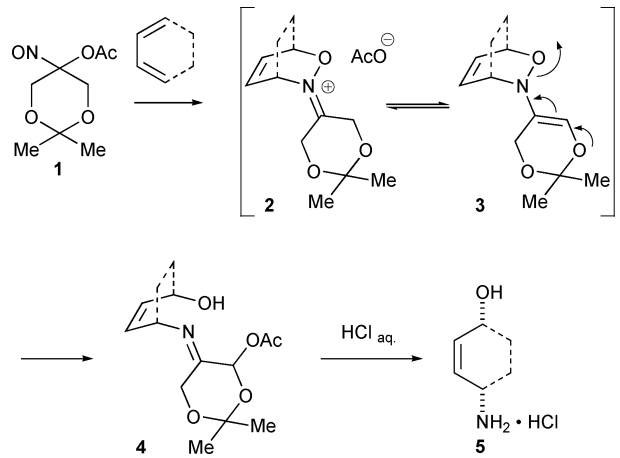
The efficient cleavage of the N–O bond of some nitroso Diels–Alder cycloadducts has been achieved in mild conditions, mediated either by 2,2-dimethyl-1,3-dioxan-5-one or 1,3-dithiolane-2-carboxaldehyde. These new and purely organic conditions allow an excellent tolerance with respect to many functional groups that would have been affected by previous reductive cleavage conditions.

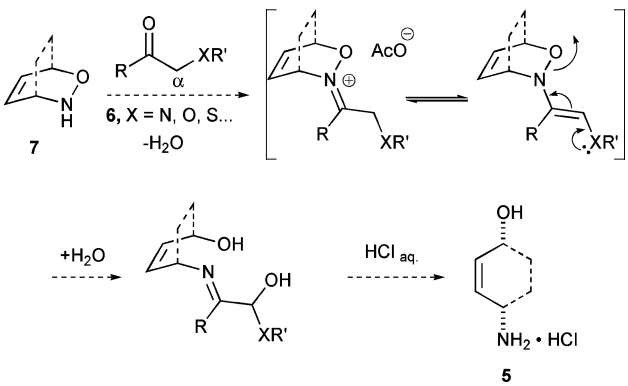
Introduction

3,6-Dihydro-1,2-oxazines are valuable synthetic intermediates that have found applications in numerous total syntheses of biologically relevant targets due to the regio- and stereoselectivity of the nitroso Diels–Alder reaction. Thus the cycloadduct may be used as a temporary protection of the functionalities then created and be further deprotected or transformed selectively in the synthesis, *via* most usually the reductive cleavage of the N–O bond of the six-membered heterocycle.[1] The numerous methods that have been developed for the cleavage of the N–O bond can be listed under three different types: (a) radical-mediated,[2] (b) anionic-mediated (with[3] or without[4] quaternarization reaction of the nitrogen atom) and (c) metal-mediated. The latter class includes the majority of the reduction conditions, based on sodium or aluminium amalgam,[5] zinc in acetic acid,[6] $LiAlH_4$,[7] molybdenum[8] or samarium[9] complexes, indium[10] and catalytic hydrogenation over Pd/C, $Pd(OH)_2$, PtO_2 or Raney Ni.[11] Some of the previous methods require harsh reaction conditions (such as strongly acidic medium at elevated temperature)[6] or lead to undesired side-reactions and/or rearrangements.[12] On the other hand, some reductive methods do not allow the selective N–O bond cleavage in the presence of other reducible functional groups.

During the course of our studies concerning the recently developed nitroso Diels–Alder dienophile **1**, we observed an unexpected N–O bond cleavage of the cycloadduct, which afforded the 1,4-*cis* aminoalcohols **5** in good yields (Scheme 1).[13] The broad synthetic interest of the obtained 1,4-*cis* aminoalcohols **5** combined with the mild reaction conditions led us to further investigate the direct conversion observed with the cycloaddition conditions. Actually, we wondered whether the condensation of a carbonyl derivative bearing a heteroatom in the α position such as **6** (Scheme 2) with a cyclic hydroxylamine derivative like **7** might



Scheme 1 Tandem [4 + 2] cycloaddition/N–O bond cleavage.[13]



Scheme 2 Proposed organic N–O σ bond heterolysis.

produce such a heterolytic N–O bond cleavage *via* the iminium–enamine equilibrium observed in our previous studies.[13]

Such a carbonyl derivative would selectively react with the nucleophilic nitrogen of the dihydro-1,2-oxazine and should therefore be inert towards other reducible functional groups, such as nitro or benzyloxy moieties.

For such an analogous reaction mediated only by a non-reductive organic compound, we are only aware of the previous N–O bond cleavage mediated by nitrosobenzene during a tandem aminoxylation/O–N bond heterolysis observed by Barbas and Ramachary.[14]

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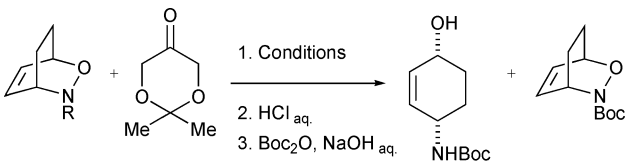
Table 1 N–O σ bond heterolysis of dihydrooxazines with ketone **9**[a]



7, R = H **9** **10** **11**
8, R = H • HCl

Entry	Reactant	Solvent	Temp/°C	Time/h	Promoter	**10** : **11**[b]	Yield (%)[c]
1	**7**	Tol.	20	14	—	0 : 100	95
2	**7**	Tol.	45	22	PPTS	100 : 0	44
3[d]	**7**	Tol.	45	22	PPTS	0 : 100	62
4	**7**	DCE	85	22	LiOAc	33 : 67	55
5	**8**	i-PrOH	20	14	—	20 : 80	100
6	**8**	i-PrOH	40	19	—	40 : 60	79
7[e]	**8**	i-PrOH	30	8	—	71 : 29	76

[a] Reaction conditions: dihydrooxazine **7** or **8**, ketone **9** (1 equivalent) under the conditions of solvent (0.15 M) and time specified in the Table. Hydrolysis with 1 N aqueous HCl followed by protection with Boc_2O in aqueous NaOH. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Isolated combined yield. [d] In the absence of ketone **9**. [e] 10 equivalents of ketone **9** were used.

In the present article, we wish to report our results concerning the efficient and general N–O bond cleavage of nitroso Diels–Alder cycloadducts mediated by some specific carbonyl derivatives such as 2,2-dimethyl-1,3-dioxan-5-one or 1,3-dithiolane-2-carboxaldehyde in mild conditions. We have shown that these conditions allow selective cleavage in the presence of some other functional groups in contrast to other previous reductive methods.

Results and discussion

N–O σ bond cleavage mediated by 2,2-dimethyl-1,3-dioxan-5-one 9

For the first experiments, commercially available ketone **9** derived from 1,3-dihydroxyacetone and 3,6-dihydro-1,2-oxazine **7** was selected, and a variety of reaction conditions were screened (Table 1).‡

In the absence of promoters, no reaction occurred at 20 °C and thus, after NBOC protection for analysis and further product isolation, **11** was obtained in 95% yield (entry 1). A slight increase of the temperature to 45 °C and the addition of one equivalent of pyridinium *para*-toluenesulfonate led, after NBOC protection for chromatographic isolation, to an encouraging 44% yield of the hydroxycarbamate **10** (Table 1, entry 2). Although this yield was still moderate, this result clearly showed that the desired N–O bond cleavage might be achieved, mediated by a suitable ketone such as **9** in a pure organic medium, requiring no added reducing agent. In the absence of ketone **9**, after NBOC protection, **11** was isolated only in 62% yield, indicating that substantial decomposition occurred under this set of conditions (Table 1, entry 3). Switching from the Brϕnsted acid PPTS to the Lewis acid LiOAc in 1,2-dichloroethane at 85 °C increased only moderately the conversion (Table 1, entry 4).

The limited stability of 3,6-dihydro-1,2-oxazine **7** under this set of conditions and the poor solubility of PPTS in toluene prompted us to examine other reaction conditions. Taking these considerations into account, 3,6-dihydro-1,2-oxazinium chloride **8** might have the advantage of catalyzing the formation of the desired iminium **2**, immediate precursor of the postulated key intermediate **3** for cleavage (Scheme 1). When 3,6-dihydro-1,2-oxazinium chloride **8** was reacted with one equivalent of ketone **9** in iPrOH at 20 °C for 14h, a **10** : **11** ratio of 20 : 80 was obtained in quantitative yield after protection (Table 1, entry 5). Increasing the temperature to 40 °C for 19 h led to a **10** : **11** ratio of 40 : 60 (Table 1, entry 6). TLC monitoring of the reaction mixture showed that ketone **9** was rapidly disappearing presumably due to some hydrolysis of the ketal, even when **9** was used in large excess (Table 1, entry 7, **10** : **11** = 71 : 29, 76%). Such competitive ketal deprotection could not be avoided under the preceding acidic conditions, therefore requiring an α-heteroatom substituted carbonyl derivative, which should be stable in the reaction conditions, in order to optimize the desired cleavage.

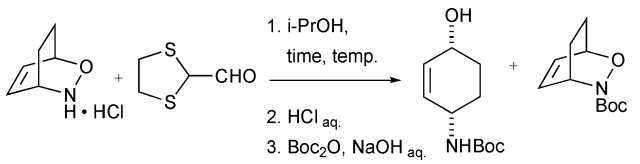
N–O σ bond cleavage mediated by 1,3-dithiolane-2-carboxaldehyde 12

1,3-Dithiolane-2-carboxaldehyde **12** was selected as reactant, due to its stability in the acidic conditions used previously and to its greater electrophilicity compared to ketone **9**. Aldehyde **12** was conveniently prepared on a multigram scale by DIBAH reduction of commercially available ethyl 1,3-dithiolane-2-carboxylate.[15]

When 3,6-dihydro-1,2-oxazinium chloride **8** was reacted with one equivalent of aldehyde **12** in i-PrOH (0.15 M) at 30 °C for 4.5 h, a **10** : **11** ratio of 77 : 23 was obtained (Table 2, entry 1). The best yield was then obtained with 1.5 equivalents of aldehyde **12** (0.15 M) in iPrOH, at 40 °C for 30 h (97% conversion), or more conveniently at 50 °C after 4.5 h (86% isolated yield, Table 3, entry 4).

‡ Simpler carbonyl derivatives (including commercially available dihydroxyacetone dimer and [1,3]-dithiane-2-carbaldehyde prepared according to P. C. Bulman Page, A. P. Marchington, L. J. Graham, S. A. Harkin and W. W. Wood, *Tetrahedron*, 1993, **49**, 10369) were also evaluated in these studies. Inferior results and/or complex mixtures were obtained.

Table 2 N–O σ bond heterolysis of dihydrooxazines with aldehyde **12**[a]



8 **12** **10** **11**

Entry	Temp/°C	Time/h	**10** : **11**[b]	Yield (%)[c]
1[d]	30	4.5	77 : 23	65
2	30	20	89 : 11	94
3	40	30	97 : 3	94
4	**50**	**4.5**	**98 : 2**	**86**

[a] Reaction conditions: dihydrooxazinium chloride **8**, aldehyde **12** (1.5 equivalents) in i-PrOH (0.15 M). Hydrolysis with 1 N aqueous HCl followed by protection with Boc_2O in aqueous NaOH. [b] Determined by ^1H NMR and/or GC analysis of the crude reaction mixture. [c] GC yield calibrated *versus* an internal standard (butylphthalate). [d] 1 equivalent of aldehyde **12** was used.

Scope of the N–O σ bond cleavage mediated by 1,3-dithiolane-2-carboxaldehyde 12

We next examined the scope of this new cleavage of the N–O bond of dihydrooxazinium hydrochlorides, mediated by the aldehyde **12** (Table 3).

Under the previously defined optimal conditions, 1,2-oxazinium chloride **13** led to the corresponding 1,4-*cis*-aminoalcohol **14** in an excellent 88% yield for two steps (Table 3, entry 1). Aromatic substituents in the 6-position of the 1,2-oxazinium chloride allow a clean and efficient cleavage as long as the aromatic ring is not too electron-rich. Actually, 1,2-oxazinium chloride **15** led to a complex mixture under our standard N–O bond cleavage conditions (Table 3, entry 2), and extensive attempts to try to optimize the formation of the desired cleavage product were unsuccessful. On the other hand, 1,2-oxazinium chloride **17** bearing a *meta*-bromo aryl substituent underwent a smooth N–O bond cleavage, affording after NBOC protection, the desired hydroxycarbamate in 77% isolated yield (Table 3, entry 3). It is worth noting that such a C–Br bond would not be compatible with some of the previously reported N–O bond reductive cleavage, such as some catalytic hydrogenations, or sodium amalgam for example.[16] Another functional group incompatible with the classical conditions is the nitro group. The latter is readily reduced by $LiAlH_4$, Zn–AcOH or under catalytic hydrogenation conditions.[17] Only a few examples of N–O σ bond reduction in the presence of a nitro group are known.[18] In contrast, when 1,2-oxazinium chloride **19** bearing a *para*-nitro phenyl substituent was treated with [1,3]-dithiolane-2-carbaldehyde **12** for 2.5 h at 50 °C, a clean N–O bond scission occurred, leading after NBOC protection, to the desired hydroxycarbamate **20** in 76% isolated yield (Table 3, entry 4).

Conclusions

We have shown that some carbonyl compounds having an α-hetero substituent, such as 2,2-dimethyl-1,3-dioxan-5-one or preferably 1,3-dithiolan-2-carboxaldehyde, react with 1,2-oxazinium salts to achieve efficiently in mild conditions the cleavage of the N–O bond. The corresponding 1,4-*cis* aminoalcohols were isolated in good to excellent yield, without metal contamination, inherent to classical reducing methods. The scope of this purely organic N–O bond cleavage has been studied and the only current limitation appeared to be dihydrooxazinium chlorides bearing electron-rich aromatic rings as substituents in the 6-position of 3,6-dihydro-1,2-oxazinium hydrochlorides. This new method of cleavage should be compatible with many functional groups that tolerate the moderately acidic conditions described. This method should also be of interest for the selective cleavage of the N–O bond of tetrahydro-1,2-oxazines, which are more difficult to achieve for example by Al(Hg), Na(Hg) or even samarium iodide. We are currently exploring the scope of this organomediated N–O bond cleavage for acyclic N–O as well as N–N σ bonds in general.

Experimental

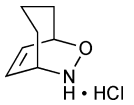
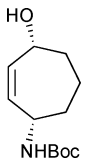
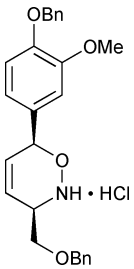
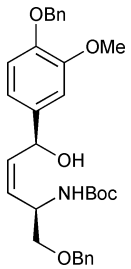
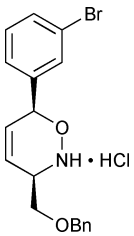
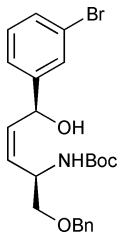
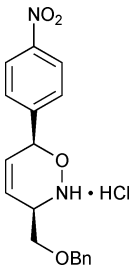
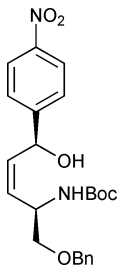
General experimental

All reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of dry nitrogen. All solvents were purified before use unless otherwise indicated. Tetrahydrofuran, diethyl ether and toluene were distilled over sodium–benzophenone ketyl anion under argon. Dichloromethane was distilled over CaH_2 under argon. All other reagents were purchased and used without further purification. Solvent removal was performed at reduced pressure using a rotary evaporator with water aspiration. Analytical thin layer chromatography (TLC) was performed on glass plates precoated with a 0.25 mm thickness of Kieselgel 60 F254. The TLC plates were visualized by shortwave UV light, potassium permanganate, *p*-anisaldehyde or ceric ammonium molybdate stain. Flash chromatography was performed according to the method of Still on Kieselgel 60 (230–400 mesh) silica gel. Infrared spectra were recorded as thin films on NaCl plates using a Perkin–Elmer Spectrum One FT-IR spectrophotometer. ^1H NMR spectra were measured at 300 MHz on Bruker Advance 300. Melting points were recorded on a Büchi 510 melting point apparatus. Chemical shifts are reported in δ units to 0.01 ppm precision, with coupling constants reported in Hertz to 0.1 Hz precision using residual chloroform (δ 7.27 ppm) as an internal reference. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, bs = broad singlet. ^{13}C NMR spectra were measured at 75 MHz using $CDCl_3$ (δ 77.0 ppm) as an internal reference. Mass spectra were performed at the Institut de Chimie des Substances Naturelles (ICSN, CNRS, Gif sur Yvette, France). Compounds **7**,[19] **8**,[20] **12**[15] and **13**[21] were prepared according to literature procedures. The spectroscopic data of compounds **10**, **11** and **14** obtained in these studies were identical to those reported in the literature.[13]

(2*E*,4*E*)-5-(4-Benzyloxy-3-methoxy-phenyl)-penta-2,4-dienoic acid ethyl ester (22)

To a solution of triethyl phosphonocrotonate[22] (5.0 mL, 22.6 mmol) and 3-methoxy-4-benzyloxy benzaldehyde **21** (5.47 g, 22.6 mmol) in THF (38 mL) was added molecular sieves (powdered 4 Å, 6.0 g) and $LiOH{\cdot}H_2O$ (1.0 g, 23.7 mmol) under vigorous stirring. The suspension was warmed at 45 °C for 3 h, cooled to room temperature, filtered on a Büchner funnel and the filtrate was diluted with water. The aqueous phase was extracted with EtOAc

Table 3 Scope of the N–O σ bond heterolysis of dihydrooxazines[a]

Entry	Oxazinium chloride		Time/h	Product		Yield (%) [b]
1		**13**	4.5		**14**	88
2		**15**	2–24		**16**	—
3		**17**	2.5		**18**	77
4		**19**	2.5		**20**	76

[a] Reaction conditions: dihydrooxazinium chloride, aldehyde **12** (1.5 equivalents except for entry 4, 1.4 equivalents) in i-PrOH (0.15 M, except for entry 4, 0.05 M) at 50 °C. Hydrolysis with 1 N aqueous HCl followed by protection with Boc_2O in aqueous NaOH. [b] Isolated yield.

and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 90 : 10 to 80 : 20) to give 6.67 g (87%) of compound **22** as a thick yellow oil that slowly crystallised.

Mp: 77 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.46–7.39 (6 H, *Ph* + C*H*=CH); 7.04–6.80 (5 H, *Ar* + *CH*=*CH*); 5.97 (1 H, d, *J* 15.3, CH=C*H*); 5.20 (2 H, s, OCH_2Ph), 4.25 (2 H, q, *J* 7.2, OCH_2CH$_3$); 3.95 (3 H, s, OCH_3); 1.33 (3 H, t, *J* 7.2 Hz, OCH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 167.2 (CO), 149.7 (Ar. Quat.), 149.1 (Ar. Quat.), 144.8, 140.3, 136.7 (Ar. Quat.), 129.5, 128.6, 127.9, 127.2, 124.4, 121.0, 120.2, 113.5, 109.5, 70.8 (Ph*C*H$_2$O), 60.3 (CH$_3$*C*H$_2$OCO), 56.0 (O*C*H$_3$), 14.3 (*C*H$_3$CH$_2$OCO). LRMS (ES): *m*/*z* (%) = 361.1 ([M + Na]$^+$, 100), 436.1 (34). HRMS (ES, Na$^+$): calculated for $C_{21}H_{22}O_4Na$ [M + Na]$^+$: 361.1416, found: 361.1428.

1-Benzyloxy-4-((1*E*,3*E*)-5-benzyloxy-penta-1,3-dienyl)-2-methoxy-benzene (23)

To a solution of ester **22** (6.66 g, 19.7 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added DIBAL (1.5 M in toluene, 29.0 mL, 43.3 mmol). The solution was slowly warmed to room temperature over 1 h and transferred carefully to a saturated aqueous solution of potassium and sodium tartrate (100 mL) *via* canula. Diethyl ether (200 mL) was added and vigorous stirring was continued until both phases were clear. The aqueous phase was extracted with EtOAc and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 80 : 20 to 60 : 40) to give 5.26 g (79%, 2 steps) of the desired alcohol as a white solid (mp: 86 °C, LRMS (ES): *m*/*z* (%) = 319.1 ([M + Na]$^+$, 100), 267.1 (43), 320.1 (7), 228.1 (3); HRMS

(ES, Na^+): calculated for $C_{19}H_{20}O_3Na$ [M + Na]$^+$: 319.1310, found: 319.1306).

The latter compound (4.50 g, 15.18 mmol) was dissolved in DMF (15 mL) and cooled to 0 °C. NaH (purum, 0.47 g, 19.7 mmol) was then added. After 10 min, BnBr (2.0 mL, 16.7 mmol) was added dropwise and the reaction mixture was warmed to room temperature. After 12 h, the solution was hydrolyzed with water (70 mL) and the aqueous phase was extracted with a cyclohexane–CH_2Cl_2 solution (90 : 10, 3 × 60 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 95 : 5) to give 4.04 g (69%) of compound **23** as a pale yellow oil that slowly crystallized to white crystals.

Mp: 43 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.50–7.30 (10 H, 2 × *Ph*); 7.01 (1 H, d, *J* 1.7, *H Ar*); 6.90 (1 H, dd, *J* 1.7 and 8.2, *H Ar*); 6.84 (1 H, d, *J* 8.2, *H Ar*); 6.70 (1 H, dd, *J* 10.5 and 15.2, Ar–CH=C*H*–CH=CH–CH_2); 6.52 (1 H, d, *J* 15.2, Ar–C*H*=CH–CH=CH–CH_2); 6.42 (1 H, m, Ar–CH=CH–C*H*=CH–CH_2); 5.92 (1 H, dt, *J* 6.1 and 15.2, Ar–CH=CH–CH=C*H*–CH_2); 5.19 (2 H, s, CH_2OCH_2Ph); 4.57 (2 H, s, ArOCH_2Ph); 4.14 (2 H, d, *J* 6.1, Ar–CH=CH–CH=CH–CH_2); 3.94 (3 H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 149.6 (Ar. Quat.), 148.0 (Ar. Quat.), 138.2 (Ar. Quat.), 137.0, 133.2, 132.5 (Ar. Quat.), 130.7, 129.1, 128.5, 128.4, 127.8, 127.75, 127.6, 127.2, 126.6, 119.6 (Ar), 113.8 (Ar), 109.1 (Ar), 72.0 (CH_2O), 70.9 (CH_2O), 70.5 (CH_2O), 55.9 (OCH_3). LRMS (ES): *m*/*z* (%) = 459.2 (40), 443.2 (24), 425.2 (45), 358.2 (14), 357.1 (100).

(3*R*,6*S*)-6-(4-Benzyloxy-3-methoxy-phenyl)-3-benzyloxymethyl-3,6-dihydro-[1,2]oxazine-2-carboxylic acid *tert*-butyl ester (24)

To a solution of 1,3-diene **23** (2.27 g, 5.80 mmol) and *tert*-butyl-*N*-hydroxycarbamate[20] (0.78 g, 5.80 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added Bu_4NIO_4 (2.51 g, 5.8 mmol) portionwise over 30 min. After 1 h 30 min at 0 °C, additional BocNHOH (0.2 g, 1.50 mmol) and Bu_4NIO_4 (0.4 g, 0.92 mmol) were added. The reaction mixture was then hydrolyzed with water and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with a 10% aqueous $Na_2S_2O_3$ solution, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 95 : 5 to 90 : 10) to give 2.15 g (71%) of compound **24** as a yellow oil that crystallized slowly to white crystals. 372 mg of 1,3-diene **23** (16%) were also recovered.

Mp: 97 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.46–7.28 (10 H, 2 × *Ph*); 6.93 (1 H, s, Ar.); 6.87 (2 H, s, Ar.); 6.10 (1 H, ddd, *J* 2.2, 4.3 and 10.3, OCH–C*H*=CH–CHN); 5.99 (1 H, br. d., *J* 10.3, OCH–CH=C*H*–CHN); 5.50 (1 H, br. s, OC*H*–CH=CH–CHN or OCH–CH=CH–C*H*N); 5.19 (2 H, s, CH_2OCH_2Ph); 4.76 (1 H, br. s., OC*H*–CH=CH–CHN or OCH–CH=CH–C*H*N); 4.65 (1 H, d, *J* 12.0, ArOCH_2Ph); 4.60 (1 H, d, *J* 12.0, ArOCH_2Ph); 3.87 (3 H, s, OCH_3); 3.84 (1 H, dd *J* 7.2 and 9.7, CH_2OCH_2Ph); 3.71 (1 H, dd *J* 6.2 and 9.7, CH_2OCH_2Ph); 1.55 (9 H, s, OC(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 154.4 (Ar. Quat.), 149.5 (Ar. Quat.), 148.5 (Ar. Quat.), 138.0 (Ar. Quat.), 136.8 (Ar. Quat.), 129.9, 128.8, 128.4, 128.2, 127.7, 127.4, 127.0, 124.7, 120.8 (Ar.), 113.5 (Ar.), 111.8 (Ar.), 81.5 (O*C*Me$_3$), 78.3 (O*C*HPh), 73.1 (O*C*H_2Ph), 70.8 (O*C*H_2Ph), 70.5 (*C*H_2OCH$_2$Ph), 55.8 (*C*H_3O), 53.7 (br, *C*HN), 28.2 (O*C*Me$_3$). LRMS (ES): *m*/*z* (%) = 540.2 ([M + Na]$^+$, 100), 484.2 (90), 485.2 (13), 440.2 (18). HRMS (ES, Na^+): calculated for $C_{31}H_{35}NO_6Na$ [M + Na]$^+$: 540.2386, found: 540.2362.

(3*R*,6*S*)-6-(4-Benzyloxy-3-methoxy-phenyl)-3-benzyloxy-methyl-3,6-dihydro-2*H*-[1,2]oxazin-2-ium chloride (15)

To a solution of dihydrooxazine **24** (0.30 g, 0.58 mmol) in dioxane (1 mL) at 0 °C was added HCl (4 N in dioxane, 0.58 mL, 2.32 mmol). White crystals precipitated after 1 h at 0 °C. After filtration, the solids were washed with pentane and dried under high vacuum to give 0.178 g (68%) of the desired **15** as white crystals.

Mp: 143 °C (decomp.). ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 7.47–7.30 (10 H, 2 × *Ph*); 7.01 (1 H, d, *J* 8.1, Ar.); 6.94–6.88 (2 H, Ar.); 6.23 (1 H, br. dt, *J* 1.3 and 10.8, OCH–CH=C*H*–CHN); 6.13 (1 H, ddd, *J* 1.9, 4.3 and 10.8, OCH–C*H*=CH–CHN); 5.81 (1 H, br. d, *J* 1.7, OC*H*–CH=CH–CHN or OCH–CH=CH–C*H*N); 5.15 (2 H, s, ArOCH_2Ph); 4.67 (2 H, s, CH_2OCH$_2$Ph); 4.33 (1 H, m, OC*H*–CH=CH–CHN or OCH–CH=CH–C*H*N); 3.83–3.79 (5 H including 3.80 (3 H, s, OCH_3), CH_2OCH$_2$Ph). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 151.2 (Ar. Quat.), 150.9 (Ar. Quat.), 138.6 (Ar. Quat.), 138.3 (Ar. Quat.), 130.4, 129.5, 129.2, 129.1, 129.0, 128.6, 122.8, 120.8 (Ar.), 115.1 (Ar.), 113.5 (Ar.), 81.6 (O*C*Me$_3$), 74.4 (O*C*HPh), 71.8 (O*C*H_2Ph), 67.5 (O*C*H_2Ph), 56.6 (*C*H_2OCH$_2$Ph or *C*H_3O), 55.8 (*C*H_2OCH$_2$Ph or *C*H_3O). LRMS (ES): *m*/*z* (%) = 440.1 ([M − Cl + Na]$^+$, 100), 418.2 (28), 409.2 (22). HRMS (ES, Na^+): calculated for $C_{26}H_{28}NO_4Na$ [M − Cl + Na]$^+$: 441.1916, found: 441.1903.

(2*E*,4*E*)-5-(3-Bromo-phenyl)-penta-2,4-dienoic acid ethyl ester (26)

To a suspension of 3-ethoxycarbonylallylidenetriphenyl-arsonium bromide[23] (2.0 g, 4 mmol) in THF (10 mL) was added *n*-BuLi (2.5 M in hexanes, 1.6 mL, 4 mmol) dropwise at 0 °C. The red solution was stirred for 30 min at that temperature. 3-Bromobenzaldehyde (0.23 mL, 2 mmol) was then added and the reaction mixture was stirred for 1 h at 0 °C and 1 h at room temperature before being quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with EtOAc and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 90 : 10) to give 339 mg (60%) of compound **26** as a slightly yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.62 (1 H, t, *J* 1.7, *H* Ar.); 7.47–7.37 (2 H, Ar.); 7.28–7.21 (2 H); 6.92–6.78 (2 H, Ar–C*H*=C*H*–CH=CH–CO); 6.04 (1 H, d, *J* 15.3, Ar–CH=CH–CH=C*H*–CO); 4.25 (2 H, q, *J* 7.2, OCH_2CH_3); 1.33 (3 H, t, *J* 6.9, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 166.9 (CO), 143.8, 138.4, 138.1, 131.7, 130.3, 129.8, 127.6, 125.8, 122.4, 60.5 (O*C*H_2CH$_3$), 14.3 (OCH$_2$*C*H$_3$). LRMS (ES): *m*/*z* (%) = 598.0 (14), 473.0 (14), 438.2 (19), 416 (19), 237 (100).

1-((1*E*,3*E*)-5-Benzyloxy-penta-1,3-dienyl)-3-bromo-benzene (27)

To a solution of ester **26** (0.275 g, 0.98 mmol) in CH_2Cl_2 (4.9 mL) at 0 °C was added DIBAL (1.5 M in toluene, 1.57 mL, 2.35 mmol). The solution was slowly warmed to room temperature over 1 h and transferred carefully to a saturated aqueous solution of

potassium and sodium tartrate *via* canula. Diethyl ether (30 mL) was added and vigorous stirring was continued until both phases were clear. The aqueous phase was extracted with EtOAc and the combined organic phases were dried over magnesium sulfate, filtered and concentrated to give a colorless oil that was used without purification in the next step. The residue was dissolved in DMF (4.9 mL) and cooled to 0 °C. NaH (purum, 47 mg, 2 mmol) was then added. After 10 min, BnBr (0.175 mL, 1.47 mmol) was added dropwise and the reaction mixture was warmed to room temperature. After 12 h, the solution was hydrolyzed with water (10 mL) and the aqueous phase was extracted with a cyclohexane–CH_2Cl_2 solution (90 : 10, 3 × 30 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 99 : 1 to 95 : 5) to give 223 mg (69%, 2 steps) of compound **27** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.55 (1 H, t, *J* 1.9, Ar.); 7.42–7.30 (7 H, Ph + Ar.); 7.19 (1 H, t, *J* 7.8, Ar.); 6.80 (1 H, dd, *J* 10.0 and 15.0, Ar–C*H*=CH–CH=CH–CH_2O); 6.51–6.40 (2 H, Ar–CH=C*H*–C*H*=CH–CH_2O); 5.97 (1 H, dt, *J* 6.2 and 15.0, Ar–CH=CH–CH=C*H*–CH_2O); 4.57 (2 H, OC*H*$_2$Ph); 4.14 (2 H, d, *J* 6.2, C*H*$_2$OCH$_2$Ph). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 132.3, 131.3, 130.9, 130.3, 130.1, 129.6, 129.1, 128.4, 127.8, 127.7, 125.0, 122.8, 122.0, 72.2 (CH_2OCH_2Ph), 70.2 (*C*H$_2$OCH$_2$Ph). LRMS (ES): *m*/*z* (%) = 459.3, 441.3, 425.3, 385.2, 357.3, 331.3.

(3*R**,6*S**)-3-Benzyloxymethyl-6-(3-bromo-phenyl)-3,6-dihydro-[1,2]oxazine-2-carboxylic acid *tert*-butyl ester (28)

To a solution of 1,3-diene **27** (0.22 g, 0.67 mmol) and *tert*-butyl-*N*-hydroxycarbamate[20] (0.13 g, 1.0 mmol) in CH_2Cl_2 (3.4 mL) at 0 °C was added Bu_4NIO_4 (0.29 g, 0.67 mmol) portionwise over 30 min. After 2 h at 0 °C, additional Bu_4NIO_4 (0.29 g, 0.67 mmol) was added portionwise over 30 min. The reaction mixture was then hydrolyzed with a saturated aqueous solution of NH_4Cl and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 90 : 10) to give 515 mg (61%) of compound **28** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.52–7.47 (2 H, Ar.); 7.37–7.21 (7 H, Ar. + Ph); 6.10 (1 H, ddd, *J* 2.4, 4.5 and 10.5, OCH–C*H*=CH–CHN); 5.93 (1 H, dt, *J* 1.4 and 10.5, OCH–CH=C*H*–CHN); 5.50 (1 H, br. s, OC*H*–CH=CH–CHN); 4.72 (1 H, br. s, OCH–CH=CH–C*H*N); 4.64 (1 H, d, *J* 11.9, PhC*H*$_2$OCH$_2$); 4.59 (1 H, d, *J* 11.9, PhC*H*$_2$OCH$_2$); 3.82 (1 H, dd, *J* 7.2 and 9.8, PhCH$_2$OC*H*$_2$); 3.69 (1 H, dd, *J* 6.2 and 9.8, PhCH$_2$OC*H*$_2$); 1.53 (9 H, s, OC(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 154.4 (CO), 139.2 (Ar. Quat.), 138.0 (Ar. Quat.), 132.0, 131.1, 130.2, 128.3, 127.6, 126.8, 125.2, 122.6 (Ar. Quat.), 81.9 (O*C*(CH$_3$)$_3$), 77.8 (*C*HO), 73.2 (Ph*C*H$_2$O), 70.5 (HN–*C*H$_2$O), 53.7 (*C*HN), 28.3 (OC(*C*H$_3$)$_3$). LRMS (ES): *m*/*z* (%) = 482.1 ([M + Na]$^+$, 57), 428.0 (93), 426.0 (100). HRMS (ES, Na^+): calculated for $C_{23}H_{26}BrNO_4Na$ [M + Na]$^+$: 482.0943, found: 482.0964.

(3*R**,6*S**)-3-Benzyloxymethyl-6-(3-bromo-phenyl)-3,6-dihydro-2*H*-[1,2]oxazin-2-ium chloride (17)

To a solution of dihydrooxazine **28** (0.345 g, 0.75 mmol) in dioxane (1 mL) at 0 °C was added HCl (4 N in dioxane, 0.75 mL, 3 mmol). White crystals precipitated after 1 h at 0 °C. After filtration, the solids were washed with pentane and dried under high vacuum to give 0.234 g (79%) of the desired **17** as white crystals.

Mp: >160 °C (decomp.). ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 7.65–7.57 (2 H, Ar.); 7.44–7.32 (7 H, Ar. + Ph); 6.24 (1 H, dt, *J* 1.4 and 10.7, OCH–CH=C*H*–CHN); 6.16 (1 H, ddd, *J* 1.9, 4.3 and 10.7, OCH–C*H*=CH–CHN); 5.88 (1 H, br. s, OC*H*–CH=CH–CHN or OCH–CH=CH–C*H*N); 4.66 (2 H, s, PhC*H*$_2$O); 4.35 (1 H, m, OC*H*–CH=CH–CHN or OCH–CH=CH–C*H*N); 3.88–3.77 (2 H, CHN–C*H*$_2$O). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 138.4 (Ar. Quat.), 134.2, 132.4, 131.9, 129.7, 129.6, 129.2, 129.1, 128.4, 123.7, 122.6 (Ar. Quat.), 121.2, 80.8 (*C*HOAr), 74.4 (Ph*C*H$_2$OCH$_2$), 67.4 (PhCH$_2$O*C*H$_2$), 55.8 (*C*HN). LRMS (ES): *m*/*z* (%) = 385.0 (13), 384.0 (92), 382.0 ([M − HCl + Na]$^+$, 100), 362.1 (8), 360.2 (8), 353.0 (12), 351.0 (12). HRMS (ES, Na^+): calculated for $C_{18}H_{18}BrNO_2Na$ [M − HCl + Na]$^+$: 382.0419, found: 382.0430.

[(*Z*)-(1*R**,4*S**)-1-Benzyloxymethyl-4-(3-bromo-phenyl)-4-hydroxy-but-2-enyl]-carbamic acid *tert*-butyl ester (18)

To a suspension of dihydrooxazinium chloride **17** (59 mg, 0.15 mmol) in i-PrOH (1 mL) was added [1,3]-dithiolane-2-carbaldehyde[3] (30 mg, 0.22 mmol) *via* a syringe. The reaction mixture became homogeneous at 30–35 °C and was stirred at 50 °C for 2 h 30 min. The solution was then cooled to room temperature and hydrolyzed with aqueous HCl (1 N, 0.5 mL). After 15 min, aqueous NaOH (3 N) was added dropwise until pH > 10 and a solution of Boc_2O (65 mg, 0.3 mmol) in THF (2 mL) was then added. The reaction mixture was stirred 12 h at room temperature, diluted with water and extracted with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 70 : 30 to 50 : 50) to give 53 mg (77%) of compound **18** as a white solid.

Mp: 52–53 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.58 (1 H, br. s, Ar.); 7.43–7.19 (8 H, Ph + Ar.); 5.75 (1 H, dd, *J* 8.6 and 10.7, OCH–C*H*=CH–CHN); 5.67–5.58 (2 H, OCH–CH=C*H*–CHN + N*H*/O*H*); 5.28 (1 H, br. d, *J* 6.4, C*H*O); 4.80–4.70 (2 H, C*H*N + N*H*/O*H*); 4.60 (1 H, d, *J* 11.9, OC*H*$_2$Ph); 4.55 (1 H, d, *J* 11.9, OC*H*$_2$Ph); 3.66 (1 H, dd, *J* 3.8 and 9.3, C*H*$_2$OCH$_2$Ph); 3.54 (1 H, dd, *J* 4.5 and 9.3, C*H*$_2$OCH$_2$Ph); 1.47 (9 H, s, OC(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 156.0 (CO), 145.3 (Ar. Quat.), 137.4 (Ar. Quat.), 134.8, 130.1, 129.8, 129.0, 128.8, 128.5, 128.0, 127.7, 124.5, 122.4 (Ar. Quat.), 80.5 (O*C*(CH$_3$)$_3$), 73.4 (*C*HO), 71.2 (Ph*C*H$_2$OCH$_2$), 67.4 (PhCH$_2$O*C*H$_2$), 47.6 (*C*HN), 28.3 (OC(*C*H$_3$)$_3$). LRMS (ES): *m*/*z* (%) = 487.1 (10), 486.1 (98), 484.1 ([M + Na]$^+$, 100), 428.0 (18), 384.1 (13). HRMS (ES, Na^+): calculated for $C_{23}H_{28}BrNO_4Na$ [M + Na]$^+$: 484.1099, found: 484.1082

(2*E*,4*E*)-5-(4-Nitro-phenyl)-penta-2,4-dienoic acid ethyl ester (30)

To a solution of triethyl phosphonocrotonate[23] (1.46 mL, 6.6 mmol) and 4-nitrobenzaldehyde **29** (1.0 g, 6.6 mmol) in THF (11 mL) was added molecular sieves (powdered 4 Å, 1.0 g) and $LiOH·H_2O$ (0.29 g, 6.9 mmol) under vigorous stirring. The suspension was warmed at 45 °C for 10 min, cooled to room temperature, filtered through Celite® and rinsed thoroughly with

diethyl ether. The black filtrate was diluted with water and the aqueous phase was extracted with EtOAc, the combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 90 : 10 to 80 : 20) to give 613 mg (40%) of compound **30** as a yellow crystals.

Mp: 101 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.24 (2 H, d, *J* 8.8, O_2N–C=C*H*–CH=C × 2); 7.61 (2 H, d, *J* 8.8, O_2N–C=CH–C*H*=C × 2); 7.45 (1 H, dd, *J* 9.8 and 15.3, Ar–CH=CH–C*H*=CH–CO); 7.01–6.91 (2 H, Ar–C*H*=C*H*–CH=CH–CO); 6.11 (1 H, d, *J* 15.3, Ar–CH=CH–CH=C*H*–CO); 4.26 (2 H, q, *J* 7.2, OCH_2CH_3); 1.34 (3 H, t, *J* 7.2, OCH_2CH_3). Spectroscopic data identical with the reported NMR.[23] LRMS (ES): *m*/*z* (%) = 518.2 (8), 517.2 (100). HRMS (ES, Na^+): calculated for $C_{26}H_{26}N_2O_8Na$ [2M + Na]$^+$: 517.1587, found: 517,1593.

1-((1*E*,3*E*)-5-Benzyloxy-penta-1,3-dienyl)-4-nitro-benzene (31)

To a solution of ester **30** (2.89 g, 12.5 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added DIBAL (1.5 M in toluene, 18.3 mL, 27.5 mmol). The solution was slowly warmed to room temperature over 1 h and transferred carefully to a saturated aqueous solution of potassium and sodium tartrate (100 mL) *via* canula. Diethyl ether (200 mL) was added and vigorous stirring was continued until both phases were clear. The aqueous phase was extracted with EtOAc and the combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 70 : 30) to give 1.49 g (58%) of the desired alcohol. The latter compound (1.49 g, 7.27 mmol) was dissolved in DMF (18 mL) and cooled to 0 °C. NaH (purum, 0.26 g, 10.9 mmol) was then added. After 10 min, BnBr (1.12 mL, 9.4 mmol) was added dropwise and the reaction mixture was warmed to room temperature. After 12 h, the solution was hydrolyzed with water (70 mL) and the aqueous phase was extracted with a cyclohexane–CH_2Cl_2 solution (90 : 10, 3 × 60 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–toluene–ethyl acetate = 80 : 20 : 0 then 50 : 50 : 0 then 50 : 40 : 10) to give 1.07 g (50%) of compound **31** as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.20 (2 H, d, *J* 8.8, O_2N–C=C*H*–CH=C × 2); 7.53 (2 H, d, *J* 8.8, O_2N–C=CH–C*H*=C × 2); 7.40–7.19 (5 H, *Ph*); 6.97 (1 H, dd, *J* 10.5 and 15.7, Ar–CH=C*H*–CH=CH–CH_2O); 6.61 (1 H, d, *J* 15.7, Ar–C*H*=CH–CH=CH–CH_2O); 6.51 (1 H, dd, *J* 10.7 and 15.0, Ar–CH=CH–C*H*=CH–CH_2O); 6.08 (1 H, dt, *J* 5.3 and 15.0, Ar–CH=CH–CH=C*H*–CH_2O); 4.47 (2 H, s, OCH_2Ph); 4.18 (2 H, dd, *J* 0.7 and 5.3, CH_2OCH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 146.7 (O_2N–*C*=CH–CH=C), 143.7, 138.1, 133.7, 132.7, 131.5, 130.0, 128.4, 127.7, 126.7, 124.0, 72.4 (CH_2OCH_2Ph), 70.0 (CH_2OCH_2Ph). LRMS (ES): *m*/*z* (%) = 352.1 ([M + Na]$^+$, 100), 350.1 (41), 279.1 (9).

(3*R**,6*S**)-3-Benzyloxymethyl-6-(4-nitro-phenyl)-3,6-dihydro-[1,2]oxazine-2-carboxylic acid *tert*-butyl ester (32)

To a solution of 1,3-diene **31** (1.0 g, 3.40 mmol) and *tert*-butyl-*N*-hydroxycarbamate[20] (0.45 g, 3.40 mmol) in CH_2Cl_2 (17 mL) at 0 °C was added Bu_4NIO_4 (0.74 g, 1.70 mmol) portionwise over 30 min. After 1 h 30 min at 0 °C, additional BocNHOH (0.2 g, 1.50 mmol) and Bu_4NIO_4 (0.4 g, 0.92 mmol) were added. The latter addition was repeated 4 times. The reaction mixture was then hydrolyzed with water and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with a 10% aqueous $Na_2S_2O_3$ solution, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 80 : 20 to 60 : 40) to give 0.69 g (48%) of compound **32** as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.10 (2 H, d, *J* 8.4, O_2N–C=C*H*–CH=C × 2); 7.42 (2 H, d, *J* 8.4, O_2N–C=CH–C*H*=C × 2); 7.29–7.18 (5 H, *Ph*); 6.04 (1 H, ddd, *J* 2.1, 4.3 and 10.4, CHO–C*H*=CH–CHN); 5.82 (1 H, br. d, *J* 10.4, CHO–CH=C*H*–CHN); 5.56 (1 H, br. s, C*H*O–CH=CH–CHN); 4.65 (1 H, br. s, CHO–CH=CH–C*H*N); 4.55 (1 H, d, *J* 12.0, CH_2OCH_2Ph); 4.50 (1 H, d, *J* 12.0, CH_2OCH_2Ph); 3.75 (1 H, dd, *J* 7.2 and 9.7, CH_2OCH_2Ph); 3.62 (1 H, dd, *J* 6.0 and 9.7, CH_2OCH_2Ph); 1.44 (9 H, s, $OC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 154.1 (CO), 147.7 (O_2N–*C*=CH–CH=C), 143.8 (Ar. Quat.), 137.6 (Ar. Quat.), 128.5, 128.1, 127.4, 125.2, 123.5, 81.9 ($OC(CH_3)_3$), 76.3 (C*H*O), 72.9 (CH_2OCH_2Ph), 70.0 (CH_2OCH_2Ph), 53.6 (CHN), 28.0 ($OC(CH_3)_3$). LRMS (ES): *m*/*z* (%) = 449.2 (18), 394.1 (6), 393.1 (100), 349.1 (3). HRMS (ES, Na^+): calculated for $C_{23}H_{26}N_2O_6Na$ [M + Na]$^+$: 449.1689, found: 449.1668.

(3*R**,6*S**)-3-Benzyloxymethyl-6-(4-nitro-phenyl)-3,6-dihydro-2*H*-[1,2]oxazin-2-ium chloride (19)

To a solution of dihydrooxazine **32** (0.65 g, 1.52 mmol) in dioxane (1 mL) at 0 °C was added HCl (4 N in dioxane, 1.5 mL, 9.1 mmol). From the purple solution, pink crystals precipitated after 1 h at 0 °C. After filtration, the solids were washed with pentane and dried under high vacuum. Recrystallization from EtOH gave 0.308 g (56%) of the desired **19** as light pink crystals.

Mp: >170 °C (decomp.). ^{1}H NMR (300 MHz, CD_3OD), δ (ppm): 8.22 (2 H, d, *J* 8.4, O_2N–C=C*H*–CH=C × 2); 7.62 (2 H, d, *J* 8.4, O_2N–C=CH–C*H*=C × 2); 7.44–7.33 (5 H, *Ph*); 6.24 (1 H, br. d, *J* 10.7, CHO–C*H*=CH–CHN or CHO–CH=C*H*–CHN); 6.18 (1 H, ddd, *J* 1.7, 3.8 and 10.7, CHO–C*H*=CH–CHN or CHO–CH=C*H*–CHN); 6.05 (1 H, br. s, C*H*O); 4.67 (2 H, s, $PhCH_2OCH_2$); 4.38 (1 H, m, C*H*N); 3.88 (1 H, dd, *J* 4.3 and 11.0, $PhCH_2OCH_2$); 3.83 (1 H, dd, *J* 6.5 and 11.0, $PhCH_2OCH_2$). ^{13}C NMR (75 MHz, CD_3OD), δ (ppm): 150.1 (O_2N–*C*=CH–CH=C), 142.9 (Ar. Quat.), 138.6 (Ar. Quat.), 130.5, 129.6, 129.4, 129.3, 129.2, 125.0, 121.4, 80.4 (*C*HO), 74.4 (CH_2OCH_2Ph), 67.5 (CH_2OCH_2Ph), 55.8 (*C*HN). LRMS (ES): *m*/*z* (%) = 350.1 (30), 349.1 (100), 327.1 (8), 318.1 (12), 188.1 (4). HRMS (ES, Na^+): calculated for $C_{18}H_{18}N_2O_4Na$ [M − HCl + Na]$^+$: 349.1164, found: 349.1162.

[(*Z*)-(1*R**,4*S**)-1-Benzyloxymethyl-4-hydroxy-4-(4-nitro-phenyl)-but-2-enyl]-carbamic acid *tert*-butyl ester (20)

To a suspension of dihydrooxazinium chloride **19** (25 mg, 0.07 mmol) in i-PrOH (1.4 mL) was added [1,3]-dithiolane-2-carbaldehyde[3] (14 mg, 0.10 mmol) *via* a syringe. The reaction mixture became homogeneous at 40 °C and was stirred at 50 °C for 2 h 30 min. The solution was then cooled to room temperature, hydrolyzed with aqueous HCl (1 N, 0.5 mL). After 15 min, aqueous

NaOH (3 N) was added dropwise until pH > 10 and a solution of Boc_2O (30 mg, 0.14 mmol) in THF (2 mL) was then added. The reaction mixture was stirred for 12 h at room temperature, diluted with water and extracted with diethyl ether. The combined organic phases were dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane–ethyl acetate = 80 : 20 to 70 : 30) to give 22.3 mg (76%) of compound **20** as a white solid.

Mp: 103 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.18 (2 H, d, *J* 8.8, O_2N–C=C*H*–CH=C × 2); 7.54 (2 H, d, *J* 8.8, O_2N–C=CH–C*H*=C × 2); 7.42–7.33 (6 H, *Ph* + O*H*/N*H*); 5.78–5.61 (3 H, HNCH–C*H*=C*H*–CHOH + O*H*/N*H*); 5.28 (1 H, br. d, *J* 6.9, C*H*O); 4.75 (1 H, m, C*H*N); 4.60 (1 H, d, *J* 11.9, CH_2OCH_2Ph); 4.54 (1 H, d, *J* 11.9, CH_2OCH_2Ph); 3.67 (1 H, dd, *J* 4.1 and 9.3, CH_2OCH_2Ph); 3.55 (1 H, dd, *J* 4.5 and 9.3 CH_2OCH_2Ph); 1.46 (9 H, s, $OC(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 156.1 (CO), 150.5 (Ar. Quat.), 147.0 (Ar. Quat.), 137.3 (Ar. Quat.), 134.1, 129.6, 128.5, 128.0, 127.8, 126.6, 123.5, 80.7 ($OC(CH_3)_3$), 73.5 (*C*HO), 71.1 (CH_2OCH_2Ph), 67.3 (CH_2OCH_2Ph), 47.6 (*C*HN), 28.3 ($OC(CH_3)_3$). LRMS (ES): *m*/*z* (%) = 452.2 (11), 451.2 (100), 396.1 (4), 395.1 (53). HRMS (ES, Na^+): calculated for $C_{23}H_{28}N_2O_6Na$ $[M + Na]^+$: 451.1845, found: 451.1833.

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